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CONTENTS

Continued overleaf

CONTENTS (*continued*)

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Section of Experimental Medicine and Therapeutics

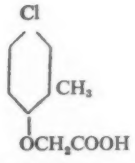
President—Professor R. A. McCance, M.D., Ph.D., F.R.C.P., F.R.S.

[*February* 12, 1952]

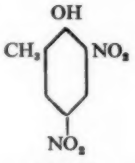
DISCUSSION ON AGRICULTURAL POISONS

R. A. E. Galley, Ph.D., A.R.C.S., D.I.C., F.R.I.C.: *The Place of Dinitrophenols and Organophosphorus Compounds in Agriculture.*

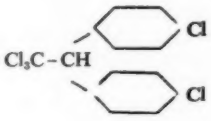
During the war interesting biological properties were found in organic compounds in which they had hitherto been unsuspected, and many of them have been introduced into agricultural practice. Very different chemical structures are represented.



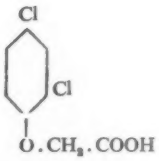
MCPA
4-chloro-2-methylphenoxyacetic acid



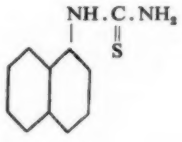
DNOC
2-methyl-4:6-dinitrophenol



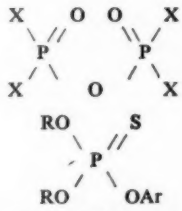
*pp'*DDT
1:1:1-trichloro-2:2-d(*p*-chlorophenyl)-ethane



2,4-D
2:4-dichlorophenoxyacetic acid



ANTU
α-naphthylthiourea



Organic derivatives of thiophosphoric and pyrophosphoric acids

It is not, however, my purpose to discuss recent advances in herbicides, insecticides and fungicides in general, but to focus attention on two groups of them, which have been "in the news", and to indicate the role they play in present agricultural practice.

The two groups of compounds are the dinitrophenols and the organo-phosphorus compounds. I will refer mainly to dinitro-ortho-cresol as typical of the first group.

3:5–*Dinitro-ortho-Cresol.*

This has been used in horticulture as a winter spray for fruit trees for some time. As far as I am aware no reports of ill-effects from its use in this way have been received. Its use as a herbicide is of more recent introduction in this country, its appearance on any appreciable scale beginning towards the end of the war.

Not many years ago the only method of destroying weeds was mechanical and took place while land was lying fallow or during the preparation of the land before sowing. When "cleaning crops" were grown, e.g. roots, inter-row cultivation could take place while the crop was growing and weeds could be kept down in this way. The system of lying fallow for a season has been largely discarded in favour of shorter spells of spring or autumn cleaning, as improvements in implements and the use of tractor power, coupled with the more recently introduced chemical weed-killers, make it possible to keep the land clean without resorting to an expensive and unproductive year. In present world conditions we must use every acre of land as efficiently as possible.

Let us trace briefly the history of chemical weed control. The first attempts at chemical weed control in growing crops, as opposed to the use of arsenicals, sodium chlorate and phenolic compounds for removing all vegetation, e.g. from paths, railway tracks, &c., began in the early part of this century. Up to the 1920's dusts of calcium cyanamide and potassium chloride and dilute solutions of copper sulphate were applied to control the broad-leaved weeds in cereals.

These particular compounds were not very efficient and, if applied heavily to ensure killing the weeds, frequently caused damage to the crops, as the degree of selectivity between crop and weed was insufficient.

Between 1920 and 1930 dilute sulphuric acid came into the picture, introduced originally in France. It is still used to a limited extent for this purpose, or should I say was used until the sulphur shortage caused its virtual elimination.

Dilute sulphuric acid is, however, very highly corrosive and, as the average farmer is not so good at cleaning out his spray equipment as he might be, the costs of repairs to spray gear were very high.

The next advance, again from France, came in the early thirties. This was the discovery that dinitro-o-cresol (DNOC) was a selective weed-killer. Although a dangerous compound, concerning which we shall hear more later, it has been used for many years with success on cereal crops, in the form of its sodium or ammonium salts, with and without ammonium sulphate.

I should like to repeat here that for many years dinitro-o-cresol has been used as a winter wash on fruit. It is used at roughly one-tenth the concentration required for weed killing, but it is applied in very large volumes. It is of interest that no case of any effect on health has, as far as I am aware, been reported as a result of this operation.

The next outstanding discovery in this field was the incredible phytotoxicity of some of the so-called "growth hormones" when applied in excessive quantities. When I say excessive, I mean in excess of the minute quantities which are produced naturally or are added to stimulate root growth or induce fruit set.

At a few pounds per acre, some of these compounds, e.g. 4-chloro-2-methylphenoxyacetic acid and 2:4-dichlorophenoxyacetic acid, cause high mortalities of many weeds. These discoveries were made in England by Templeman and his collaborators in 1940.

Although experiments have shown that chemical weed control can be undertaken with several crops (e.g. in carrots, with oil; in peas, with 2:4-dinitro-6-sec-butylphenol; and in fact these treatments are now carried out commercially), by far the largest acreages under routine commercial treatment are the cereal crops.

The acreage of cereal crops sprayed and dusted during 1951 was about one-quarter of the total area under cereals and it is estimated that in 1952 it will be about one-third.

An estimate of the areas sprayed and dusted with different herbicides and the areas likely to be sprayed in 1952 are given below:

Herbicide		Acreage 1951	Acreage 1952
MCPA	Sprays	1,292,000	1,803,000
2,4-D	Sprays	300,000	600,000
DNOC	Sprays	114,000	130,000
MCPA and 2,4-D	Dusts	25,000	20,000

It will be seen therefore that the acreage sprayed with DNOC is but a small proportion of the total sprayed area.

It is, however, necessary to use it where corn marigolds, corn poppies, mayweeds, camomile, cleavers and fumitory have to be killed as DNOC is the only spray material at present available which

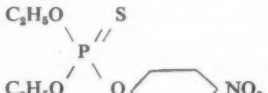
will achieve an economic control. New formulations of existing materials and different times of application may be found to bring these resistant weeds under control by known compounds less toxic to man.

In addition new compounds will, I am sure, be discovered which will ultimately enable us to do without DNOC as a herbicide.

Until then, however, in order to obtain the optimum yield of cereals, DNOC will have to be used where these weeds, which are resistant to MCPA and 2, 4-D (DCPA) are present in large numbers.

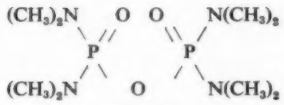
Organo-phosphorus Group.

The other group of compounds to which I must refer is the organo-phosphorus group from which I will select parathion for discussion, drawing attention to differences in properties of parathion and other members of the group as necessary. One particularly interesting difference between parathion and schradan, is the ease with which the latter is picked up by the leaves or roots of plants and translocated in the sap stream where it remains toxic, particularly to sucking insects, for some weeks.



Parathion

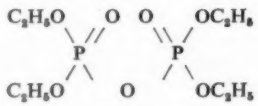
OO–diethyl O–p–nitrophenyl thionphosphate



Schradan

bisdimethylaminophosphonous anhydride

The main difference between parathion and tepp is in the speed of hydrolysis which affects the duration of any "toxic residue". Parathion and tepp are toxic to a very wide range of insects, but they are used in agriculture mainly for the control of aphids and mites. There is no doubt whatsoever that 0·01% solutions of parathion will control red spider on fruit trees to an extent impossible to achieve by other means. The fact that, when it is used in this way it may cause, in some circumstances, a temporary shift in the biological equilibrium by killing insects which are the predators of the red spiders, is outside the scope of this discussion.



Tepp

tetraethyl pyrophosphate

The Equipment by which the Weed-killers and the Insecticides are Applied to the Crops.

A trend over the last few years has been towards the use of what is called "low volume" machinery. This, as its name implies, involves the use of smaller volumes of more concentrated materials than were hitherto regarded as standard practice. It will be apparent that in order to achieve the same sort of uniformity of distribution with a small volume, the particle size of the spray must be very much smaller. All spray equipment produces a range of particle sizes and therefore the smaller particles of the low volume sprays are generally accompanied by smaller airborne particles which, if the operator is not careful, may surround him in a cloud and may be inhaled.

Low-volume machines have been designed both for ground crops and for fruit. For the latter purpose, particularly where large fruit trees are concerned, some of the machines depend upon the use of a large volume of air accompanying the spray to carry it to its target.

To minimize drift when ground crops are sprayed some designers have produced cowls to cover spray booms and to reduce the magnitude of the airborne cloud but its complete elimination is almost impossible.

To summarize, therefore: the reason why these compounds are used in agriculture is that they will perform functions which it is not possible so far to perform with other compounds. It is my personal view that new compounds will be developed which will possess the useful biological properties of these dangerous compounds without the hazard to man, but until such time as they are freely available I submit that the use of the more dangerous compounds with, of course, the relatively simple safeguards which their use demands, is justified in order that the maximum possible yield of food is obtained.

D. R. Davies, M.Sc., F.R.I.C.: *The Effect of Organo-phosphorus Insecticides on Enzymes.*

I propose to limit my contribution to three substances, OO-diethyl O-p-nitrophenyl thionphosphate (E.605 or parathion), bisdimethylaminophosphonous anhydride (Ompa, Pestox III or Schradan) and bis-isopropylamino-fluorophosphine oxide (Isopestox). This latter compound was put on the market, but for reasons which will be apparent during the course of this symposium, was withdrawn.

The properties which make these substances effective as insecticides are also those which make them toxic to man. In 1950, 198 cases of poisoning by the organic phosphorus insecticides were reported in the *Journal of the American Medical Association* (1950), 8 of them were fatal. These figures are probably much fewer than those that actually occurred.

Each of these compounds is toxic because they inhibit the enzyme cholinesterase and acute deaths are due to acetylcholine poisoning. The tissues of both men and animals poisoned with parathion and OMPA show a marked depression of the blood and tissue esterases (Grob *et al.*, 1947; DuBois *et al.*, 1950).

Neither parathion nor OMPA is a potent *in vitro* inhibitor of cholinesterase. They are converted by the liver into an active metabolite which is a powerful anticholinesterase. Thus DuBois *et al.* (1950) incubated liver slices with OMPA and showed that with increasing times of incubation, the reaction mixture became increasingly active, as an inhibitor, towards rat brain cholinesterase. They also showed hepatectomy reduced the toxicity of OMPA. This was confirmed by Cheng (1951). Early workers thought that parathion was a very powerful *in vitro* inhibitor. Diggle and Gage (1951*a*), however, showed that such activity could almost certainly be attributed to isomers of parathion which were present as impurities in the commercial substance and suggested that the anticholinesterase activity of this substance was *in vivo* and not *in vitro*. Goldblatt, quoted by Diggle and Gage (1951*b*) showed that the toxicity of parathion was reduced by hepatectomy. Aldridge and Davidson (1952) examined a particularly pure specimen of parathion and showed that its *in vitro* activity was considerably less than had been hitherto believed. Thus it is fairly certain that both of these substances are similar, in that they are both *in vivo* inhibitors of cholinesterase. There is no information available concerning the chemical nature of the active metabolite.

Earlier, I mentioned bis-isopropylamino-fluorophosphine oxide (Isopestox). This substance has now been withdrawn. I am, however, mentioning it, because recently two people were accidentally poisoned with it and they exhibited unexpected symptoms of flaccid paralysis, very similar in character to ginger paralysis which is caused by tri-ortho-cresyl phosphate—TOCP.

This compound (Isopestox) is a potent *in vitro* inhibitor of cholinesterase with a marked affinity for the pseudo-enzyme.

Too little information is available to express any views concerning the mode of action of this compound, but a clinical condition similar to that referred to above has been produced experimentally in chickens by David (1951) and Barnes and Denz (1951) using Isopestox, a condition which Barnes has also produced with DFP. Earl and Thompson (1952) using tri-ortho-cresyl phosphate have produced similar effects also in chickens, a result which had been obtained previously by Smith and Lillie in 1931 and Van Itallie Harmsma and Van Esvald in 1932. There is only one comment I would like to make at this stage. Each of these three substances is much more highly selective to the plasma or pseudo-enzyme than to the true. Much more work needs to be done before the significance of this can be assessed.

The toxicity of these substances is so great, that no discussion of this kind can be complete without a brief summary of the value of cholinesterase levels of the blood as a guide to their safe handling. My colleagues and I have investigated the significance of cholinesterase levels in relation to insecticide poisoning. As a consequence we feel that we can make a number of firm statements about blood esterase levels:

(1) Whatever the route of absorption, the ChE levels of the blood are the most convenient measure of organic phosphorus poisoning: further, departures from normal cholinesterase levels can be recognized before the onset of symptoms.

(2) A lowered esterase level in the blood indicates an increased sensitivity to subsequent absorption of insecticide.

(3) The very early symptoms of phosphorus insecticide poisoning (headache, nausea, &c.) are very commonplace. Blood cholinesterase levels are therefore of great value in the differential diagnosis of insecticide poisoning.

The ability to use esterase levels as a guide to the recognition of phosphorus insecticide absorption turns upon the accuracy with which departures from normal esterase values can be recognized. Callaway, Rutland and I (1951) investigated the variation of the cholinesterases of both the cells and plasma of a normal healthy adult population and have determined the limits of variation not only in the general population (i.e. from person to person) but also in the personal variation, i.e. in the same person. The population limits of the red-cell enzyme levels are 92 to 143 units in a service population and 75 to 142 units in a civilian population, whilst those of the plasma enzyme are 51 to 128 units.

In investigating the personal variation we were conscious of the practical issues behind the investigation and therefore asked ourselves a specific question namely, what must be the difference between two estimations of enzyme to indicate departure from the normal? This difference was obtained as a result of an investigation of a group of 10 men who were examined eight times over a period of four weeks. A full account of the results have been described elsewhere (Callaway *et al.*, 1951). For the present purpose a difference of more than 20% between two estimates of the red-cell enzyme may be taken as evidence of an abnormal deviation (the percentage being calculated on the higher of the two estimates). The corresponding figure for the plasma enzyme was 15%.

Dr. Barnes and I (1951) applied these findings to the examination of a group of factory and agricultural workers who were engaged in the manufacture and spraying of these substances. Three criteria were utilized:

(1) *Departures from normal population levels of the red-cell enzyme.*—3 men, factory workers, were found whose red-cell enzyme fell outside normal population limits; the levels were 73, 69, and 70 units and are 2, 7 and 5 units below the lower normal limit. These deviations are admittedly small but it should be emphasized that they are quite significant statistically. None of the three men exhibited any clinical symptoms.

(2) *Departures from normal population limits of the plasma enzyme.*—5 cases were encountered in which the plasma enzyme was outside normal limit; the plasma levels were 49, 46, 48, 45 and 44 units and the individuals were an agricultural sprayer, a research worker and 3 factory workers respectively. Again there was no clinical evidence of poisoning.

(3) The application of the third criterion was possible because we had been able to *estimate levels of the plasma enzyme on more than one occasion.* A difference of more than eighteen units indicates abnormal variation. It was possible to recognize abnormal deviation in 8 workers who had been examined more than once. Significant deviations were observed in 4 of these who were showing recovery from the effects of previous absorption of insecticide. They were 27, 27, 38 and 22 units and were noted in two sprayers and two chemical workers. The remaining 4 cases showed evidence of absorption during interval between routine determinations and the differences were 24, 25, 19 and 28 units; they were observed in a sprayer, two chemical workers and a laboratory worker respectively.

These cases demonstrate quite clearly the value of blood cholinesterase levels in the recognition of the systemic absorption of the organic phosphorus insecticides. The determination of blood esterase levels can be of considerable help in promoting the safe use of these materials.

These substances are undoubtedly toxic; nevertheless they may be used with safety. In conclusion may I quote from a recent paper written by Dr. Barnes and myself (1951), because in the following words we have summed up our views concerning the toxicity of these substances to man, under field conditions.

"These facts demonstrate quite clearly that the organo-phosphorus insecticides may be manufactured and applied without risk, provided manufacturer, consumer and their employees co-operate by the rigid adherence to every form of safety device and procedure which has been developed for that end.

"The observations here reported provide no grounds for complacency, and those who use or are responsible for encouraging the use of these materials should remember that freedom from accidents in this country during the past year has been the result of the heed given to early warnings rather than to the innocuous nature of the materials handled."

Acknowledgment is made to the Chief Scientist, Ministry of Supply, for permission to publish this paper.

REFERENCES

ALDRIDGE, W. N., and DAVIDSON, A. N. (1952) *Biochem. J.*, **51**, 62.
BARNES, J. M., and DENZ, F. A. (1951) Personal communication.
——, and DAVIES, D. R. (1951) *Brit. med. J.* (ii), 816.
CALLAWAY, S., DAVIES, D. R., and RUTLAND, J. P. (1951) *Brit. med. J.* (ii), 812.
CHENG, K. K. (1951) *Brit. J. exp. Path.*, **32**, 444.
DAVID, A. (1951) Personal communication.
DIGGLE, W. M., and GAGE, J. C. (1951*a*) *Biochem J.*, **49**, 491.
—, —— (1951*b*) *Nature, Lond.*, **168**, 998.
DUBOIS, K. P., DOULL, J., and COON, J. M. (1950) *J. Pharmacol.*, **99**, 376.
EARL, C. J., and THOMPSON, R. H. S. (1952) *Brit. J. Pharmacol.*, **7**, 261.
GRUB, D., LILIENTHAL, J. L., Jr., HARVEY, A. M., and JONES, B. F. (1947) *Bull. Johns Hopk. Hosp.*, **81**, 217.
VAN ITALLIE HARMSMA and VAN ESVALD (1932) *Arch. exp. Path. Pharm.*, **165**, 84.
Report to Pesticides Committee (1950) *J. Amer. med. Ass.*, **144**, 104.
SMITH, M. I., and LILLIE, R. D. (1931) *Arch. Neurol. Psychiat., Chicago*, **26**, 976.

P. Lesley Bidstrup, M.R.C.P.: *Clinical Aspects of Poisoning by Organic Phosphorus Insecticides.*

Organic phosphorus compounds already in use as insecticides include hexaethyl tetraphosphate (HETP), tetraethyl pyrophosphate (TEPP), OO-diethyl O-p-nitrophenyl thionphosphate (parathion) and bisdimethylaminophosphonous anhydride (Schradan, OMPA, Pestox-III). A new compound in this group, bis-isopropylamino-fluorophosphine oxide, has been developed, and a small quantity was manufactured by a pilot process after preliminary experiments had indicated that it would be effective as an insecticide and less toxic to mammals than some of the substances already in use (*Nature*, 1951).

The symptoms and signs of poisoning by the organic phosphorus insecticides are the same as those of poisoning by di-isopropyl fluorophosphate (DFP) and are always accompanied by reduction in the activity of the enzyme cholinesterase (ChE). Both specific cholinesterase which is present in red blood cells and nervous tissues, and pseudo-cholinesterase, which includes the various enzymes present in sera and tissues, are inhibited by these substances but the sites at which the maximum effects are produced vary with different inhibitors and in different species. Inhibition of cholinesterase by the organic phosphorus insecticides is irreversible and the recovery of normal activity of the enzyme depends upon regeneration. There is evidence that when the cholinesterase activity is below normal, an individual is unduly susceptible to the effects of any cholinesterase inhibitor. The limits of normal cholinesterase activity for the general population have been determined by Callaway, Davies and Rutland (1951). The commercial preparations of most of the organic phosphorus compounds used as insecticides inhibit cholinesterase *in vivo* and *in vitro*. OMPA does not cause inhibition of cholinesterase *in vitro* but becomes converted in the animal body, by the liver, to an active anti-cholinesterase agent (DuBois, Doull, and Coon, 1950). Diggle and Gage (1951) have shown that pure parathion is also an inhibitor of cholinesterase *in vivo* but not *in vitro*.

Inhibition of cholinesterase results in three pharmacological effects, and the symptoms and signs of poisoning by any cholinesterase inhibitor can be explained by these effects. Experiments have shown that blood cholinesterase in animals may be depressed to less than 20% of normal before symptoms of systemic poisoning appear (Barnes and Davies, 1951). There are present symptoms due to excessive stimulation of autonomic effector cells, the so-called muscarinic effects, nicotinic effects due to stimulation followed by paralysis of striate muscle, and symptoms resulting from stimulation followed by depression in the central nervous system. Not all the manifestations of each of these effects will be observed in a single case of poisoning. The physical properties of the inhibitor and the route of absorption into the body influence the site of maximum effect and account for the variety of symptoms observed in different cases. In poisoning by parathion and DFP effects upon the central nervous system are marked, whereas these are seldom observed in the case of OMPA.

Early muscarine-like symptoms include anorexia, nausea, vomiting, cramp-like abdominal pain, excessive sweating and salivation. These are followed by pallor, miosis, diarrhœa, involuntary micturition and defæcation, pulmonary œdema and cyanosis. The early symptoms of effects on the central nervous system are giddiness, apprehension, restlessness and headache. In serious poisoning ataxia, tremor, drowsiness, coma and convulsions develop. Atropine is a specific antidote to both these effects, and should be administered as soon as possible after the onset of symptoms in doses of from 1–2 mg. (1/60–1/30 grain) by intramuscular injection repeated at hourly intervals until signs of atropinization appear. The nicotinic effects are twitching of the muscles of the eyelids and tongue, spreading to affect the muscles of the face and neck and the extra-ocular muscles, and causing finally generalized muscular twitchings and marked weakness of voluntary muscles. Atropine has no effect upon these symptoms and no antidote to them is known.

In a typical case of parathion poisoning anorexia and nausea increased by smoking or taking food are followed within one-half to two hours by vomiting, cramp-like abdominal pain, salivation and sweating. Giddiness, apprehension and restlessness usually follow the onset of anorexia, but in some cases these may be the first symptoms of poisoning. Constriction of the pupils may be absent in mild cases, unless direct contact with the eyes has occurred. Muscular twitchings of the eyelids and tongue follow upon the nausea and vomiting. In serious poisoning the twitching spreads to the muscles of the face and neck and involves the extra-ocular muscles causing jerking movements of the eyes suggestive of nystagmus. Generalized muscular twitching and marked weakness of voluntary muscles may develop in spite of adequate doses of atropine, and death may occur from this neuro-muscular paralysis. In acutely ill patients diarrhœa and tenesmus and involuntary defæcation and micturition occur, and signs of broncho-constriction and pulmonary œdema are also present. The symptoms and signs of effects upon the central nervous system appear and progress with the muscarinic and nicotinic symptoms. The initial giddiness and apprehension are accompanied or soon followed by intense headache and in mild cases insomnia or unusual dreaming may be noticed. Ataxia, tremor, drowsiness and impaired powers of concentration are late symptoms and may be accompanied by mental confusion, disorientation and slurring of speech. Coma develops gradually from one to nine hours after the onset of symptoms, and generalized convulsions usually occur. Death occurs from one to twenty-one hours after the last exposure to parathion, and, on an average, nine hours after the onset of symptoms (Grob, Garlick and Harvey, 1950).

In 3 cases of acute poisoning by bis-isopropylamino-fluorophosphine oxide observed recently, muscular weakness was a striking feature of the illness. In the most severely affected patient the gastro-intestinal symptoms were most marked whereas in one less acutely ill, bronchospasm and sweating were the presenting symptoms. Constriction of the pupils was present in all 3 patients, but there were few signs of effects upon the central nervous system. These cases illustrate well the different manifestations of poisoning by the same cholinesterase inhibitor.

The treatment and prevention of poisoning by organic phosphorus compounds has been described in detail elsewhere (Bidstrup, 1950). The administration of atropine in adequate doses at the earliest stage in the course of the illness and the need to observe the patient carefully for at least forty-eight hours after the acute symptoms have subsided cannot be too strongly emphasized.

It has been stated that there are no sequelæ to poisoning by organic phosphorus compounds used as insecticides. Of the 3 people who developed acute poisoning after exposure to bis-isopropylamino-fluorophosphine oxide, 2 developed flaccid paralysis involving all four limbs which came on slowly in the third week after the acute phase of the illness. The nature of the paralysis in these cases resembles closely that which follows poisoning by tri-ortho-cresyl phosphate. Hottinger and Bloch (1943) demonstrated that tri-ortho-cresyl phosphate inhibits cholinesterase *in vitro* and *in vivo*, and is particularly effective in reducing the activity of pseudo-cholinesterase. Thompson (personal communication) has shown that bis-isopropylamino-fluorophosphine oxide also affects the pseudo-enzyme more than specific cholinesterase. The activity of both enzymes was depressed in these cases; the plasma ChE activity returned to normal more slowly than was expected by analogy with DFP (Callaway, Davies and Risley, 1952). Petry (1951) records a case of similar paralysis in a man exposed repeatedly to parathion in the fumigation of greenhouses.

These cases of delayed effects of poisoning by organic phosphorus compounds, and the experimental work of Koelle and Gilman (1946) and Hunt and Riker (1947) which demonstrated that paralysis will develop in certain species of animals following the administration of repeated sublethal doses of DFP, suggest that whereas sequelæ have not been recognized following a single, acute episode of poisoning by a cholinesterase inhibitor in man repeated exposure with persistent lowering of cholinesterase activity may lead to paralysis affecting particularly the lower limbs. I should like to emphasize that there is no conclusive evidence that this hypothesis is correct.

Since cholinesterase activity in serum and red blood cells may be reduced to more than 50% below normal activity without the appearance of symptoms, and since, when symptoms do appear, the progress from mild poisoning to serious illness or even death may occur within a few hours, it is of fundamental importance that persons at risk of absorbing even small amounts of these organic phosphorus compounds should be protected from harmful effects not only by protective devices designed to give complete protection for the particular job, but also by routine estimation of cholinesterase activity. The range of normal activity in the general population has been determined (Callaway, Davies and Rutland, 1951) and simple methods of estimation of the enzyme activity requiring only a drop of blood have been devised (Michel, 1949). Since there is a considerable individual variation in cholinesterase activity workmen at risk in factories, fields, orchards and greenhouses should have a series of estimations made before, during and after exposure to any organic phosphorus insecticide. In cases where the enzyme activity is reduced the workman should be removed from further risk until the cholinesterase activity has been demonstrated by estimation to be normal. Barnes and Davies (1951) record the blood cholinesterase levels in a group of 80 men and women exposed to organic phosphorus insecticides in the field or factory. Although strict precautions to prevent absorption of these substances were observed, 12 workers were found to have significant lowering of cholinesterase activity. The fact that none of these workers complained of symptoms which could certainly be attributed to poisoning by an anti-cholinesterase agent illustrates both the difficulty in diagnosis of poisoning on clinical evidence alone, and the value of routine cholinesterase estimations in assessing absorption of organic phosphorus compounds.

REFERENCES

Barnes, J. M., and Davies, D. R. (1951) *Brit. med. J.* (ii), 816.
Bidstrup, P. L. (1950) *Brit. med. J.* (ii), 548.
Callaway, S., Davies, D. R., and Rutland, J. P. (1951) *Brit. med. J.* (ii), 812.
——, ——, and Risley, J. E. (1952) *Biochem. J.*, **50**, xxx.
Diggle, W. M., and Gage, J. C. (1951) *Nature, Lond.*, **168**, 998.
DuBois, K. P., Doull, J., and Coon, J. M. (1950) *J. Pharmacol.*, **98**, 6.
Grob, D., Garlick, W. L., and Harvey, A. M. (1950) *Bull. Johns Hopk. Hosp.*, **87**, 106.
Hottinger, A., and Bloch, H. (1943) *Helv. chim. Acta*, **26**, 142.
Hunt, C. C., and Riker, W. F. (1947) *J. Pharmacol.*, **91**, 298.
Koelle, G. B., and Gilman, A. (1946) *J. Pharmacol.*, **87**, 435, 447.
Michel, H. O. (1949) *J. lab. clin. Med.*, **34**, 1564.
Nature, Lond. (1951) **167**, 260.
Petry, H. (1951) *Zbl. Arbeitsmed. Arbeitsschutz*, **1**, 86.
Thompson, R. H. S. (1951) Personal communication.

J. D. Judah, M.B., B.Ch., M.R.C.P.: *Mode of Action of the Nitrophenols.*

Many nitrophenols (of which 3 : 5-dinitro-ortho-cresol and 2 : 4 dinitrophenol are the best known) have the property of increasing the metabolic rate of animals poisoned with these substances.

It has been known for some time that DNOC and DNP also have the property of inhibiting the division of sea-urchin eggs, while increasing their respiration and inhibiting the synthesis of reserve materials by yeast. In recent years, the mechanism by which nitrophenols exert these effects has been clearly shown by the work of several investigators (Loomis and Lipmann, 1948; Cross, Covo, Taggart and Green, 1949; Judah and Williams-Ashman, 1951; Judah, 1951). It is now known that the inhibition of synthetic processes by these compounds is almost certainly due to their blockade of "oxidative phosphorylation".

This term should, perhaps, be more fully explained. In the familiar sequence of reactions known as the glycolytic cycle, phosphorylations occur at two points, and it can be calculated that, starting with glucose as substrate, a net gain of 2 molecules of adenosine-triphosphate (ATP) will be made. In the further oxidation of pyruvate by the tricarboxylic acid cycle (or Krebs cycle), however, the number of phosphorylations is far greater, about 30 molecules of ATP being formed per molecule of glucose completely oxidized. It is now considered most probable that the ATP so formed is the means by which cells utilize the energy of the oxidations, and a simple calculation will show that the process is some 60% efficient when studied *in vitro* and possibly the efficiency *in vivo* is greater still (*see* Judah, 1951).

The acceleration of metabolic processes by DNOC can be explained in two ways, both concerned with the phosphorylation reactions. It is known that nitrophenols acting *in vitro* on the isolated material which contains the Krebs cycle enzymes (probably the mitochondria, *see* Kennedy and Lehninger, 1948, 1949; Judah and Williams-Ashman, 1951; Judah, 1951) will accelerate the respiration of these systems when they are deficient in inorganic ortho-phosphate or in adenine-nucleotide. It is now considered likely that the cell in its ordinary state is probably a system which is deficient in both these substances, and it is considered probable that DNOC produces its accelerative effect by interrupting the phosphate transfer which involves both inorganic phosphate and adenine-nucleotide, thus making relatively more of these compounds available to the respiratory mechanism.

The probability that DNOC operates in the way described above has been investigated by my colleague Dr. P. N. Magee and myself (unpublished studies). We injected rats with lethal doses of the nitrophenol and found at varying times after injection a great fall in the creatine phosphate, adenosine-triphosphate and adenosine-diphosphate of all the tissues, usually associated with an increase in inorganic phosphate and adenylic acid. Similar studies with isolated rat diaphragms yielded the same results, and it is of interest that a progressive failure of the muscle to respond to stimulation was observed in the presence of the poisons. Complete failure and rigor developed at a time when the ATP level had reached vanishing point.

There are many gaps in our knowledge of the mechanism of action of the nitrophenols, but it seems that a reasonable explanation of their physiological effects is possible on the present information. Further work on the fundamental problems is being carried out in various laboratories including our own.

REFERENCES

Cross, R. J., Covo, G. A., Taggart, J. V., and Green, D. E. (1949) *J. biol. Chem.*, **177**, 655.
Judah, J. D. (1951) *Biochem. J.*, **49**, 271.
——, and Williams-Ashman, H. G. (1951) *Biochem. J.*, **48**, 33.
Kennedy, E. P., and Lehninger, A. L. (1948) *J. biol. Chem.*, **172**, 847.
——, —— (1949) *J. biol. Chem.*, **179**, 957.
Loomis, W. F., and Lipmann, F. (1948) *J. biol. Chem.*, **173**, 807.

P. Lesley Bidstrup, M.R.C.P.: *Clinical Aspects of Poisoning by Dinitro-ortho-Cresol.*

The late manifestations of poisoning by 3 : 5-dinitro-ortho-cresol (DNOC) are well known and have been described recently by Hunter (1950), Steer (1951) and Bidstrup and Payne (1951). They are the result of stimulation of the general metabolism and are aggravated by heat. Although the stimulation of metabolism is peripheral and independent of thyroxine (Dodds and Robertson, 1933) the clinical picture in the final stages of poisoning resembles that of thyroid crisis. No antidote to DNOC is known, and in acute poisoning death occurs within a few hours from heat stroke or cerebral œdema. The dramatic change from apparent well-being to death within an hour or so has impressed upon all who have observed these cases the need to protect workmen at risk of absorbing dangerous amounts of this substance by any route.

Experience in the use of DNOC in agriculture and horticulture in Great Britain since 1945 suggests that the men most likely to develop DNOC poisoning are contract sprayers using DNOC as a selective weed-killer on cereal crops. Eight spray operators and one man engaged in the manufacture of DNOC have died and many cases of poisoning are known to have occurred during this time, all of them in periods of unusually hot weather (Merewether, 1943; Bidstrup and Payne, 1951). No case of poisoning has been recorded among men using DNOC as a late winter wash on fruit trees.

Measures adopted to reduce the incidence of DNOC poisoning in spray operators have included

the use of protective clothing and enclosed tractor cabins to prevent absorption of the material, instruction of operators in spraying methods and in the early symptoms and signs of poisoning, and routine medical examination. These methods have not proved successful, and this is due in part to the difficulty in recognizing the earliest symptoms of DNOC poisoning.

The first of these is an exaggerated feeling of well-being. In experiments on human volunteers undertaken by the Department for Research in Industrial Medicine of the Medical Research Council, this symptom was observed on the third or fourth day in every volunteer but the significance was not fully appreciated at the time. Our attention was drawn to the importance of this as the earliest manifestation of absorption of DNOC in significant amounts by the head of a firm of contract sprayers (Hardy, 1951). He stated that when he observed this "fitter than usual" condition in an employee spraying DNOC he immediately transferred the man to other work. The change of occupation was usually resented because the man felt so well. This may be the explanation of a finding which has been emphasized frequently at inquests on fatal cases of DNOC poisoning.

In nearly all cases, the man has been made aware of the dangerous nature of the spray material and of the early symptoms of poisoning; in some a paper describing these symptoms and instructing the man to report at once to a doctor should he feel unwell has been found on the body at the time of death. It seems likely that the feeling of well-being and abounding energy leads the man to continue spraying and to absorb further amounts of DNOC which can cause fatal poisoning. Other early symptoms are sweating, thirst and fatigue but these are often attributed to hot weather and long hours of work. Yellow staining of the sclerotics indicates absorption of but not necessarily poisoning by DNOC. The palms of the hands and the soles of the feet are always more deeply stained than other parts of the skin, and for many months after the last exposure to DNOC, the distal ends of the finger-nails and toe-nails and of the hair on all parts of the body remain yellow.

Recent observations on human volunteers taking known doses of DNOC by mouth, and on process workers and spray operators at risk of absorbing DNOC by inhalation and ingestion and through the skin have made it possible to correlate physiological effects with the concentration of DNOC in the blood as determined by the method described by Parker (1949). In man DNOC is a cumulative poison which is excreted very slowly; rats and rabbits are able to metabolize it much more rapidly (King and Harvey, 1952). The administration of approximately 1 milligram per kilo to man by mouth at intervals of twenty-four hours results in a gradual increase in the concentration of DNOC in the blood which reaches its maximum in two to four hours after ingestion. When the pre-dosage level is of the order of 15 to 20 micrograms per gramme of blood, the ingestion of a further dose of 75 milligrams causes a marked rise in the concentration of DNOC in the blood. This occurs within four hours, and is associated with symptoms of lassitude, headache and general malaise. Even when no DNOC has been absorbed for five days, and the blood level is of the order of 10 micrograms per gramme, the administration of a further dose causes a sharp rise in blood DNOC and the concentration fails to return to pre-dosage level within twenty-four hours. Exercise will increase the concentration of DNOC in the blood, as will the application of DNOC to the skin. This latter effect is slight and, in our opinion, absorption of DNOC through the skin is of less importance in causing symptoms than is absorption by the other routes. Six weeks after the final dose of DNOC had been administered significant amounts could still be detected in the blood. The excretion of DNOC in the urine in twenty-four hours bears no fixed relation to the concentration of DNOC in the blood (Harvey, Bidstrup and Bonnell, 1951).

These observations on human volunteers suggested that it would be possible by estimations of blood DNOC to detect absorption of potentially dangerous amounts in workmen at risk before symptoms became obvious. In our opinion a spray operator whose blood DNOC concentration is of the order of 15–20 micrograms per gramme in a specimen of blood taken not less than eight hours after the last exposure should be removed from risk of absorbing even small amounts of DNOC. Since he will have no symptoms of poisoning he need not be taken off work altogether. Symptoms will be present when the concentration of DNOC in the blood is of the order of 40 micrograms per gramme.

The treatment of DNOC poisoning is symptomatic. It includes sedation by means of barbiturates, replacement of fluid and electrolytes, and attempts to reduce the temperature by means of a cool environment and tepid sponging (Pollard and Filbee, 1951). No antidote is known at the present time.

REFERENCES

Bidstrup, P. L., and Payne, D. G. H. (1951) *Brit. med. J.* (ii) 16.
Dodds, E. C., and Robertson, J. D. (1933) *Lancet* (ii), 352.
Hardy, F. (1951) Personal communication.
Harvey, D. G., Bidstrup, P. L., and Bonnell, J. A. L. (1951) *Brit. med. J.* (ii), 13.
Hunter, D. (1950) *Brit. med. J.* (i), 449.
King, E., and Harvey, D. G. (1952) *Biochem. J.*, **51**, vii.
Merewether, E. R. A. (1943) Annual Report of the Chief Inspector of Factories. London; p. 51.
Parker, V. H. (1949) *Analyst*, **74**, 646.
Pollard, A. B., and Filbee, J. F. (1951) *Lancet* (ii) 618.
Steer, C. (1951) *Lancet* (i), 1419.

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DISCUSSION ON THE DIAGNOSIS OF PULMONARY EMPHYSEMA

Professor J. Gough (Department of Pathology and Bacteriology, Welsh National School of Medicine, Cardiff):

The Pathological Diagnosis of Emphysema

I have used paper-mounted large sections of lung for the study of the gross anatomy of emphysema. These preparations were devised by Gough and Wentworth (1949) for the study of pneumoconiosis, and particularly to demonstrate the forms of emphysema associated with that condition. The sections have also been found useful when applied to non-industrial emphysema. Such preparations being representative of the whole lung are of value in estimating the overall severity of emphysema since the latter is very rarely of uniform degree throughout the lung and the examination of selected small areas by histological methods alone, may give a misleading impression of the total lung damage. Histological methods are, however, essential in detecting slighter degrees of emphysema, and for accuracy measurement of alveolar size as used by Hartroft and Machlin (1943, 1944) is necessary. The large sections are suitable for the assessment of moderate and severe degrees. From them can be judged how much tissue survives as well as how much has been destroyed and they show the extent of what Christie calls the "pathological dead space". The lungs were expanded by running formalin solution into the main bronchi after removal from the body. Normal lungs were treated in the same way for comparison.

The examination post mortem of a number of lungs from individuals who had been examined during life in the departments of Professor R. V. Christie and Dr. C. M. Fletcher, has demonstrated that where marked evidence of emphysema has been shown by laboratory methods, gross evidence of the condition can be seen by the naked eye in paper-mounted sections. The patterns of emphysema seen in these cases vary considerably and the large sections reveal certain distributions of bullæ which are not readily seen when the lung is examined whole or sliced in the usual way in the autopsy room.

The patterns suggest that the mechanics involved in the production of widespread chronic emphysema are not always the same and there appear to be at least two perhaps fundamentally different types. In the one, the forces at work appear to affect the lungs as one unit, whereas in the other, the disturbance seems to concern more particularly the mechanics of the individual secondary lobules. In non-industrial cases the former type of emphysema appears the more common. We find the familiar picture of bullæ most abundant and largest in the upper parts of the lung, projecting from the surface but also in severe cases occupying a considerable part of the interior of the lung. The large sections show that bullæ within the lung are frequently distributed along blood vessels, bronchi and septa. Such bullæ may be found in chains running up to the hilum. "Lack of support" is usually put forward as the reason for peripheral bullæ but this would not explain the bullæ along the main vessels and bronchi. It would seem rather that the bullæ tend to occur in relation to all parts of the framework of the lung, whether this is in the interior or on the surface. The expanding force of respiration not only disrupts the lung adjacent to the pleura, but also seems to pull the degenerate lung parenchyma from its framework in the interior of the lung.

The second characteristic distribution of bullæ is within the centres of the secondary lobules. This is the commonest type of emphysema seen in coal workers, and its anatomy is easily seen in the paper-mounted sections because there is usually sufficient dust to outline the secondary lobules and to show that the emphysema starts in the centres of these lobules round about the terminal and respiratory bronchioles which in coal workers are surrounded by collections of dust-containing cells. A similar distribution of bullæ within secondary lobules is seen in some cases of non-industrial emphysema so that the presence of a contracting coal focus is not essential for the production of this type of lesion. In the severest examples of this central lobular emphysema that I have seen in a non-dusty lung there was severe chronic inflammation of the terminal bronchioles. The presence of coal foci seems, however, to account for the great frequency of this form of emphysema in coal workers. It is probable that a disturbance of the bronchiolar mechanism is responsible. Heppleston (1951) has shown, however, that in coal workers' simple pneumoconiosis the bronchioles are not obstructed. But I think that they may be less able to expand on account of the collar of dust and reticular fibrosis that occurs around them. Heppleston (1947, 1951) considers the emphysema to be due in part to shrinkage of the coal foci together with the force of inspiration on the lung around these solid foci.

Bullous emphysema may occur in only one of the lungs or may severely affect the whole of one lobe while the rest of the lung tissue is little affected. Partial stenosis of the bronchus of one lung or one lobe seems the likely cause of this distribution.

Since bronchial obstruction is believed to play a part in the development of certain forms of emphysema, examinations of the lungs from cases of chronic spasmodic asthma would be expected to give information on obstructive emphysema. Of the cases that I have examined where death was due to status asthmaticus, I have been surprised to find that in several of them there was little evidence

of chronic irreversible emphysema. Some of the individuals had suffered from spasmodic asthma for very many years without producing bullous emphysema; in those showing the latter condition, the appearance was not distinctive and the distribution of the bullæ was similar to that seen in chronic bronchitis. It would seem that intermittent bronchiolar obstruction as in spasmodic asthma does not produce central lobular emphysema. (An incidental finding in the asthmatic lungs was the frequent occurrence of chronic localized bronchiectasis apparently due to areas of collapse. The bronchiectasis was not suspected during life.)

The condition of honeycomb lung as described by Oswald and Parkinson (1949) can usually be distinguished from bullous emphysema. These authors have suggested that the cysts resemble focal emphysema of pneumoconiosis, but I find the appearances to be different and the mechanisms of their formation may be different also. Honeycomb lung is not uncommon in coal workers and when it occurs in a lung which also shows the common focal emphysema, the differences in the two lesions are striking. Focal emphysema of coal workers may be compared to a wheel consisting of a central lesion of dust, the hub as it were, with spokes radiating between the emphysematous spaces. In the honeycomb lung, however, there are no hubs and spokes, we have only the rim. Honeycomb lung and focal emphysema are both the result of interstitial infiltrations, but in different positions. Perhaps in the former the infiltration is mainly in the septa between the secondary lobules while in the latter the infiltration is mainly around respiratory and terminal bronchioles.

In conclusion I would say that the large section technique should help in resolving the differences of opinion that so often exist between clinicians, radiologists and pathologists as to the existence and severity of emphysema in particular cases.

REFERENCES

GOUGH, J., and WENTWORTH, J. E. (1949) *J. R. micr. Soc.*, **69**, 231.

HARTROFT, W. S., and MACHLIN, C. C. (1943) *Trans. roy. Soc. Can.* S 3, **37** (Sect. V), 75.

——, —— (1944) *Trans. roy. Soc. Can.*, S 3, **38** (Sect. V), 63.

HEPPLESTON, A. G. (1947) *J. Path. Bact.*, **59**, 453.

—— (1951) *Arch. industr. Hyg.*, **4**, 270.

OSWALD, N., and PARKINSON, T. (1949) *Quart. J. med.*, **18**, 1.

Dr. C. M. Fletcher (Pneumoconiosis Research Unit, Llandough Hospital, Cardiff):

The Clinical Diagnosis of Pulmonary Emphysema—An Experimental Study

To most clinicians, the term "emphysema" conveys a picture of a patient with a functional disturbance —exertion dyspnœa—and with certain more or less characteristic signs comprising the emphysematous type of chest. With the help of the radiologist, he may sub-divide emphysema into groups such as "acute vesicular", "compensatory", "bullous" or even "unilateral" emphysema. But he cannot distinguish the various patterns of pathological change which Professor Gough has described and, in effect, the clinical diagnosis of emphysema is restricted to so-called chronic hypertrophic emphysema and comprises all breathless subjects who present certain accepted physical signs. Though the diagnosis is admittedly uncertain (Christie, 1944) it is commonly made with serene confidence. I shall now consider how far this confidence may be justified.

So far as symptoms are concerned, dyspnœa is really the only essential. Cough and sputum are the symptoms of pre-existing or consequent bronchitis. It is true that the majority of cases of emphysema give a history of cough preceding breathlessness for many years, but this is not always so, and in some severe cases, cough is either absent or is insignificant. There are probably as many causes as there are pathological patterns of emphysema, and the study of the history may assist in distinguishing them, but I am here only concerned with the clinical diagnosis and assessment of the final established condition. To do this the clinician must determine, on the one hand, the severity of dyspnœa and, on the other, the presence of the physical signs.

First then, the clinician must assess the severity of the dyspnœa. Such a subjective and comparative symptom cannot be assessed by any single simple question, such as "How breathless are you on exertion?" for the answer will largely depend upon the patient's habits and activities, and the effect of age in diminishing exercise tolerance is very great—as many of us are painfully aware—so that we cannot safely compare a man's present with his previous abilities.

The standard questions which we have for some years employed in the Pneumoconiosis Research Unit to establish clinical grades of breathlessness are as follows:

Grade 1: Is the patient's breath as good as that of other men of his own age and build at work, on walking, and on climbing hills or stairs?

Grade 2: Is the patient able to walk with normal men of own age and build on the level but unable to keep up on hills or stairs?

Grade 3: Is the patient unable to keep up with normal men on the level, but able to walk about a mile or more at his own speed?

Grade 4: Is the patient unable to walk more than about 100 yards on the level without a rest?

Grade 5: Is the patient breathless on talking or undressing, or unable to leave his house because of breathlessness?

We have found that the use of these questions has enabled different observers to get reasonably repeatable results on independent examination of random samples from a single large population of miners (Cochrane, Chapman and Oldham, 1951). There is also general agreement between the answers to these questions and an objective measure of dyspnœa (Hugh-Jones, 1952).

For most purposes, then, the clinician may rest content with the answers to such questions to determine the severity of the dyspnœa, but he must be constantly aware of the disturbing effect in individual assessments of bias which may be introduced by himself and by the patient, especially when an issue such as compensation, or the value of a favourite method of treatment, is at stake.

The assessment of the physical signs.—My colleagues and I recently carried out an experiment in collaboration with Professor Christie and his colleagues. The experiment arose out of a request by Professor Christie's group to visit the Pneumoconiosis Research Unit in order to study the physical signs in the chest in cases of pneumoconiosis for comparison with those they were accustomed to note in cases of uncomplicated emphysema attending their special Clinic. We decided to make use of this visit to study observer error in the elucidation of these physical signs. There were 8 observers,[1] all of whom were Members or Fellows of the Royal College of Physicians and they were all continually concerned in their daily work with the study of emphysema. Each observer carried out a full clinical examination of the chest on 20 patients and his findings were recorded by an amanuensis on a prepared form. Each sign was recorded as being absent, present or marked. Fifteen minutes were allowed for the examination of each subject. Although in routine clinical work this would be a generous allowance, some observers felt rushed and became tired towards the end of the experiment.

At the time of the examination, each observer was told the patient's clinical grade of breathlessness and in the light of this information and his examination, he was asked to assess the presence or absence of emphysema. Since two members of the "home team" knew some of the patients, their diagnoses of emphysema have had to be discarded from the analysis.

The characteristics of the patients are shown in Table I. It will be seen that they were all middle-aged or elderly, and pretty disabled. Half of them had massive fibrosis due to pneumoconiosis, seven had

TABLE I.—DETAILS OF 20 PATIENTS EXAMINED BY 8 OBSERVERS

No.	Age	Radiological diagnosis: Category N SP	Category PMF	Emphysema	Clinical grade	T.L.C. (ml)	R.C. %
1	49	0		++	1	6610	50
2	50	2		++	4	7370	65
3	53	0		+++	4	5740	71
4	48	1		0	2	6440	49
5	60		A	+	4	6368	55
6	65	1		+	4	5850	65
7	47	0		+	4	7300	72
8	40		C	++	3	6740	46
9	53		D	++	3	4940	29
10	51		C	++	3	4480	52
11	59		C	0	4	4260	38
12	48		B	++	4	6630	66
13	46		C	+++	3	7880	61
14	50	1		++	4	4820	69
15	57	2		+++	5	7490	74
16	47		C	+++	5	6450	61
17	39		D	+	3	3490	36
18	39		C	+++	2	5890	47
19	65	2		++	4	6280	67
20	56	1		+	3	8270	64
Mean	51	Total 10	10	++	3-5	6170	57

Category. According to International Classification (Cochrane, Davies and Fletcher, 1951).

N = No pneumoconiosis.
SP = Simple pneumoconiosis.
PMF = Progressive massive fibrosis.
T.L.C. = Total lung capacity.
R.C. = Residual capacity.

[1]Dr. C. M. Fletcher, Dr. P. Hugh-Jones, Dr. C. B. McKerrow, Dr. L. R. West, Professor R. V. Christie, Dr. D. V. Bates, Dr. J. M. S. Knott, Dr. M. B. McIlroy.

y simple pneumoconiosis and three had no evidence of pneumoconiosis. Nearly all showed some iographic evidence of emphysema. Their total lung capacities were not greatly increased, but the dual capacity percentage was very high in the majority. This residual capacity percentage is by means an absolute measure of severity of emphysema, but it is an index which is still widely epted and in the United States of America it is almost considered synonymous with emphysema. aldwin, Cournand and Richards, 1949; Motley, Gordon, Lang and Theodos, 1950). For my present rpose I have had to use it as the only available index of the severity of emphysema independent of inical assessment. By this criterion, the patients, with three exceptions, all had moderate to extremely evere degrees of emphysema, but since the majority had pneumoconiosis and half of them had massive brosis, they were not uncomplicated cases of emphysema.

These then were the patients upon whom we sought to study the observer error in the physical signs of the chest and from whom I shall attempt to derive some hesitant conclusions regarding the value of certain signs in the diagnosis of emphysema. I have chosen to study signs which were mentioned by ive out of six standard textbooks as being present in cases of emphysema. They are: barrel chest, wide sub-costal angle, kyphosis, use of accessory muscles of respiration, impaired chest expansion, movement *en bloc*, generalized hyper-resonance, impaired liver dullness, impaired cardiac dullness, absent apical impulse, impaired breath sounds.

I will now consider the differences between the observers in determining the presence or absence of these signs and in their final diagnosis of emphysema. Most of us assume that, except in occasional borderline cases, the signs we observe are present and those which we do not observe are absent. However, experiment does not support this view and great disparities become apparent. Fig. 1 shows the frequency with which each of the physical signs was detected by each observer (referred to by the letters A to H). The full height of each column shows the number of cases in which the sign was recorded as present by each observer, the double-hatched portions of the columns represent the number of cases in which the observer found the sign to be "markedly" present. It can be seen at once that there is great variation between the observers. For instance, observer C and G never considered that the accessory muscles were used in respiration in these cases, whereas A and D thought they were used in three-quarters of them. Observer H thought they were markedly used in three of them. Barrel chest was diagnosed three times as often by F as by A. Observer D stands out as being a particularly sensitive (or imaginative) observer, recording the highest frequency of positives in most of the signs. He also failed least often to detect the apical impulse.

This figure also gives a general impression of the frequency with which these abnormal physical signs were observed in this emphysematous group of subjects. Impaired chest expansion, movement *en bloc*, and absent apical impulse were common, whereas a wide subcostal angle and impaired breath sounds and hyper-resonance were less often observed.

The figure does not tell the full story of inter-individual disagreement. For instance, observers D and F observed impaired chest expansion with equal frequency, namely in 11 cases each, but only 6 of these were the same cases, and there were only 4 cases in which they both agreed the expansion was unimpaired. Thus there were 10 agreements and 10 disagreements—50% disagreement, although in Fig. 1 they appear to agree. There is no really simple method for expressing the average level of inter-individual disagreement. Perhaps the simplest method is to consider the percentage of observers who dissented from the majority in the assessment of each sign. Where the observers are equally divided, we can say that there is 50% disagreement, where they are divided into five and three, 37·5% are in disagreement with the majority, 25% disagree where the distribution is six and two and so on. For each sign we can average the percentages recorded for each of the 20 patients. The results are given in Table II, excluding those cases in whom the particular sign was never found positive, so that only those cases where disagreement could arise are considered. The percentage disagreement ranges from 19–33. In hyper-resonance (33%) the observers were divided so that on the average two thought one thing and one another, whereas in relation to impaired expansion (19%) the proportions were 4 to 1. It is important to realize that these differences in disagreement represent not only the difficulty the observers found in detecting the various signs, but they also reflect the degree to which the signs were positive in this group of cases. On the whole, the patients had grossly impaired chest expansion and the observers found less difficulty in agreeing on this point. The higher level of disagreement in diagnosing the use of accessory muscles, hyper-resonance and impaired liver dullness, may in part be due to the fact that this group of cases did not show these signs to a marked degree. It may equally be due to the fact that the observers found these signs difficult to elucidate. In the absence of any absolute opinion as to the presence or absence of the sign, we cannot disentangle these two influences.

The only sign for which we might expect to obtain an absolute opinion is impaired chest expansion, for at the end of his examination, each observer measured the chest expansion of each subject at the nipple level by means of an ordinary tape measure. There was surprising disagreement in the measurements obtained. In twelve of the subjects, the range of the measured expansion was 1 in. or more, reaching $1\frac{3}{4}$ in. in one subject. The range was never less than $\frac{1}{2}$ in. More consistent results would presumably have been obtained had we been able to provide each observer with a spring-loaded tape

measure (Cotterill, 1951). The mean of the measured expansions has been taken as the true chest expansion and in Fig. 2 the relationship between the chest expansion of each patient and the number of positive diagnoses of impaired chest expansion is plotted. It will be seen that the chest expansion was grossly impaired in all the patients; only one had an expansion of more than 2 in. Even in the patients with an expansion of 1½ in. or less, the average number of positive diagnoses was only 7 out of 8 (disagreement 12·5%). In patients with 1½ to 2 in. expansion, the average was only 5 positive diagnoses out of 8 (disagreement 37·5%).

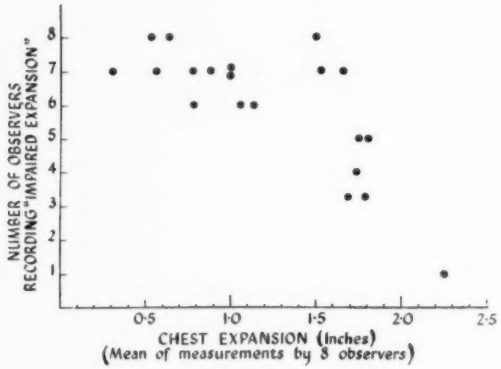

FIG. 2.

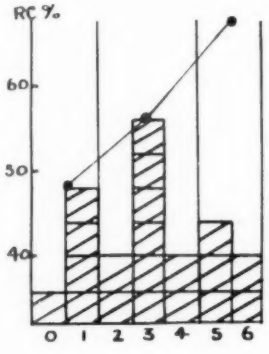

FIG. 3.

FIG. 2.—Relationship between the measured chest expansion (average of measurements of 8 observers) (abscissæ) and the number of observers recording "impaired chest expansion" (ordinates).

FIG. 3.—Frequency distribution of diagnoses of emphysema by 6 observers in 20 subjects. Each small square represents one case and the numbers on the horizontal scale give the number of positive diagnoses. The vertical scale gives the residual capacity %. The solid circles give the mean value of the residual capacity in the groups of cases separated by the vertical lines.

As students, we are taught that the cardiac impulse at the apex is either palpable or impalpable, yet there was in this group of cases a 26% chance that one of the observers would disagree with the others on this point (Table II). The errors may seem smaller if we look at the figures the other way

TABLE II.—PHYSICAL SIGNS OF EMPHYSEMA. DISAGREEMENT BETWEEN 8 OBSERVERS

Sign	Cases with at least one positive diagnosis	
	Number	% Disagreement
Barrel chest	17	29
Wide sub-costal angle	15	31
Kyphosis	17	27
Use of accessory muscles	18	31
Impaired expansion	20	19
Movement *en bloc*	19	23
Hyper-resonance	18	33
Impaired liver dullness	19	32
Impaired cardiac dullness	20	29
Absent apical impulse	20	26
Impaired breath sounds	19	29
"Emphysema"	19	29

round and state that agreement ranged from 70–80%. But we must recall that if the observers had tossed pennies to get their answers instead of examining the patients' chests, they would have got 50% agreement. 67% (for hyper-resonance) is not so very much better than this; although such a level of agreement would not be obtained once in a thousand times if pennies had been tossed instead of chest percussed. Presumably so little attention has been given by clinicians to the problem of error in assessing physical signs because they seldom hunt in couples of equal seniority. But it is nevertheless surprising and I know of no account in the literature of any previous experimental investigation of error in assessing physical signs in the chest.

FIG. 1.—Frequency of diagnosis of each physical sign by 8 observers in 20 patients and of emphysema by 6 of the observers. The full height of each column gives the number of cases in which each observer found the sign present, the double hatched portion gives the number of patients in which he found the sign "marked".

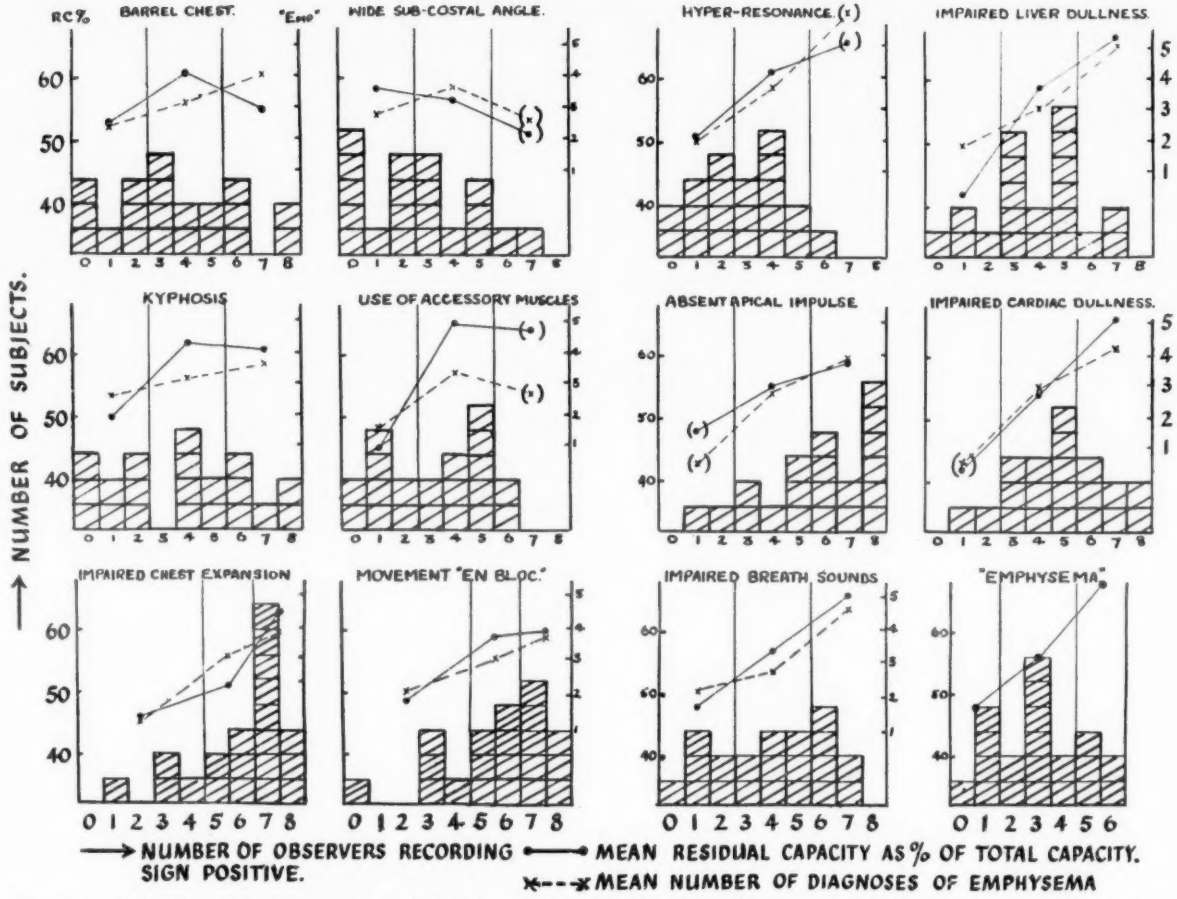

FIG. 4.—Frequency distributions of positive diagnoses of each physical sign by 8 observers on 20 patients. For details *see* legend to Fig. 3. In addition, the crosses represent the mean frequency of positive diagnoses of emphysema (by 6 observers) in the groups of cases separated by the vertical lines. (Emphysema scale on the right-hand and R.C.% scale on the left-hand side of each diagram.)

Some other fields of clinical assessment have been investigated. In laryngology, it has been shown that there is little or no agreement between different doctors in assessing the severity of tonsillar disease (Bakwin, 1945) and gross disagreements in the assessment of redness of the throat between different observers examining the same throat on the same day have been shown by Proetz (1939). Clinical assessment of the status of nutrition of children has been shown to depend more upon the observer than upon the child (Derryberry, 1938; Huws-Jones, 1938). The greatest amount of investigation has been done in the field of radiology, particularly in relation to tuberculosis (Garland, 1950; Yerushalmy *et al.*, 1950, 1951) and in pneumoconiosis (Fletcher and Oldham, 1949, 1951). Christie and Knott (1951) have also shown that the radiological diagnosis of emphysema is uncertain. Only in the field of radiology has the work been directed to discovering techniques whereby the error could be reduced.

My own results are also purely negative. They just demonstrate the magnitude of the errors but give no indication of the way in which they might be reduced. It is possible that by careful definition of some of the signs, agreement might be increased. For instance, in impaired liver and cardiac dullness, one might define more precisely the point at which the percussion note should change for a diagnosis of slightly and markedly reduced dullness. Photographs might be used for the barrel chest, protractors for the sub-costal angle and so on. If physical signs are to be used in clinical diagnosis, then their use should be made as accurate as possible and the study of the errors to which they are subject and the way in which these errors may be reduced merit more attention than they have hitherto been given.

Although the physical signs we have considered were subject to great errors in their elucidation, they may, none the less, be valid signs of emphysema. I propose now to consider the evidence provided by the experiment on this question. To do this, we must attempt to discover how far their presence or absence was or was not associated with emphysema. We are here up against the difficulty of having no absolute measure of the emphysema. I am, therefore, forced to use the percentage residual capacity although, as I have said, this is not a proper index of the severity of emphysema. There was, however, a fairly strong association between the clinical diagnoses of emphysema made by the observers and the residual capacity percentage. This is shown in Fig. 3, which gives the frequency distribution of positive diagnoses of emphysema by the six observers whose diagnoses of emphysema could be accepted as unbiased. The frequency is given in the form of a histogram showing the number of cases in which no diagnosis of emphysema was made, (1 case), in which one was made (4 cases) and so on, up to those in whom six diagnoses of emphysema were made (2 cases). Thus the cases at the left hand of the histogram were seldom diagnosed as having emphysema and those at the right hand end had emphysema diagnosed frequently. The cases may be placed into three groups, with infrequent (0–1) moderately frequent (2–4) and frequent (5–6) diagnosis of emphysema, as has been done in the figure, and we can find the mean residual air in the three groups. These values are plotted above the histogram and it is found that the residual capacity increased with the increasing frequency of the diagnosis of emphysema. We can now apply a similar technique to all the physical signs plotting frequency distributions of diagnosis and plotting the mean residual airs in three groups. We can also take for each group the mean frequency of diagnosis of emphysema. This has been done in Fig. 4. It will be seen that in the particular 20 cases whom we examined, barrel chest or wide sub-costal angle bore no relationship to the residual air percentage and very little relationship to the frequency of diagnosis of emphysema. The relationship was also relatively poor in the case of kyphosis, use of accessory muscles, impaired chest expansion and movement *en bloc*. In the other signs, the relationship was very much better, particularly in the signs concerned with hyper-resonance and the impairment of breath sounds.

This figure also gives an impression of frequency of diagnoses of these various signs in this emphysematous group of cases. Those signs with the histogram shifted to the left were relatively infrequently diagnosed, those shifted to the right were relatively frequently diagnosed. Those heaped up in the middle are the signs in which there was the greatest amount of disagreement, either because the sign was difficult to assess, or because it was present to an indifferent degree.

It is most important to emphasize that these findings only apply to the particular 20 cases who formed the material for this experiment. Half of these cases had massive fibrosis and cannot be considered typical cases of uncomplicated emphysema. Moreover, for a proper assessment of the relationship of these signs to the diagnosis of emphysema, we should study a larger group of cases ranging from complete normality to extreme abnormality. In the cases we studied, there were no subjects who could really be said to be normal and the majority were grossly abnormal.

The poor relationship of barrel chest and wide sub-costal angle to emphysema is very striking. It may be due to the fact that emphysema in cases of pneumoconiosis is not associated with the large chest of the ordinary uncomplicated emphysema. On removing the cases with massive fibrosis from the analysis, however, I found their relationship is not much altered, but the number of cases is then so small that it is impossible to be sure.

My chief purpose in presenting these findings is to suggest that an experiment of this kind may be of value in assessing the validity of physical signs for the diagnosis of any chest condition. The subjects

should be selected to illustrate every gradation from normality to abnormality in the particular condition under examination. In a properly selected group of patients, studied perhaps by a group of more skilled observers than those who partook in our experiment, it might be possible to demonstrate clearly which signs are and which are not relevant to the clinical diagnosis of emphysema. In the light of such an experiment, it might be possible to reject some of the traditional signs and we might in this way lessen the burden we at present lay upon students of medicine who have to learn so many clinical methods based upon tradition rather than upon experiment.

With regard to the clinical diagnosis of emphysema, my conclusion is that it cannot be made with any confidence (at least by a single observer) except perhaps in the most advanced cases, so that there is little hope of the clinician being able to diagnose the early stages. For this he must turn to the objective methods of the physiologist to help him in his perplexity.

ACKNOWLEDGMENTS

I should like to thank the other 7 observers for their co-operation and for permission to publish this paper, and to Dr. J. C. Gilson and Mr. P. D. Oldham for assistance in the organization and analysis of the experiment.

REFERENCES

BAKWIN, H. (1945) *New Engl. J. Med.*, **232**, 691.
BALDWIN, E. DE F., COURNAND, A., and RICHARDS, D. W. (1949) *Medicine, Baltimore*, **28**, 201.
CHRISTIE, R. V. (1944) *Brit. med. J.* (i), 143.
——, and KNOTT, J. M. S. (1951) *Lancet* (i), 881.
COCHRANE, A. L., CHAPMAN, P. J., and OLDHAM, P. D. (1951) *Lancet* (i), 1007.
——, DAVIES, I., and FLETCHER, C. M. (1951) *Brit. J. industr. Med.*, **8**, 244.
COTTERILL, M. S. (1951) *Physiotherapy*, **37**, 49.
DERRYBERRY, M. (1938) *Publ. Hlth. Rep., Wash.*, **53**, 263.
FLETCHER, C. M., and OLDHAM, P. D. (1949) *Brit. J. industr. Med.*, **6**, 168.
——, —— (1951) *Brit. J. industr. Med.*, **8**, 138.
GARLAND, L. H. (1950) *Amer. J. Roentgenol.*, **64**, 32.
HUGH-JONES, P. (1952) *Brit. med. J.* (i), 65.
HUWS-JONES, R. (1938) *J. R. Statist. Soc.*, **101**, 1.
MOTLEY, H. L., GORDON, B., LANG, L. P., and THEODOS, P. A. (1950) *Arch. industr. Hyg.*, **1**, 133.
PROETZ, A. (1939) *Ann. Otol. Rhin. Laryng.*, **48**, 176.
YERUSHALMY, J., HARKNESS, J. T., COPE, J. H., and KENNEDY, B. R. (1950) *Amer. Rev. Tuberc.*, **61**, 443.
——, GARLAND, L. H., HARKNESS, J. T., HINSHAW, H. C., MILLER, E. R., SHIPMAN, S. J., and ZWERLER, H. B. (1951) *Amer. Rev. Tuberc.*, **64**, 225.

Dr. J. C. Gilson and Mr. P. D. Oldham (Pneumoconiosis Research Unit, Llandough Hospital, Cardiff):

Lung Function Tests in the Diagnosis of Pulmonary Emphysema

The Use of Discriminant Analysis

The type of problem in which we are interested is estimating the prevalence of emphysema in miners without pneumoconiosis and in non-miners in a community, or the assessment of the degree of emphysema in the radiological stages of pneumoconiosis. We are using this latter problem to illustrate our method.

From Dr. Fletcher's communication it is clear that physical signs of emphysema are difficult to interpret and observe, and also that the diagnosis largely depends on the presence of breathlessness for which no other cause can be found. The clinician is therefore using a subjective assessment of function as his most important single criterion for diagnosis. This suggests that the objective physiological measurements of function should provide a more satisfactory index of the presence and degree of emphysema.

A variety of tests have been reported to be characteristic of emphysema. It was early observed that the residual capacity (R.C.)—the air remaining in the lung at the end of expiration—was increased in advanced cases. However, the absolute value of the residual capacity depends partly on the size of the individual, and thus it has become common to express the residual capacity as a percentage of the total lung capacity (T.L.C.) to allow for individual variations in size. A R.C.% T.L.C. greater than 36% is now often regarded as synonymous with some degree of emphysema (McCann, 1939; Motley *et al.*, 1949; Baldwin *et al.*, 1949) but recent investigations (Greifenstein *et al.*, 1952) have shown that the ratio is not independent of age, there being a considerable rise in the percentage in apparently normal elderly subjects. For example, in our series, men aged 55 had on the average a ratio 12% greater than men aged 25. This of course may indicate that there are changes in normal individuals which are the same as those which occur in emphysema. Whatever the reason, it draws attention to the necessity for comparing men of comparable age groups when using the R.C.% T.L.C. as an index of abnormality. There is another difficulty in using the ratio which is well shown in cases of

pneumoconiosis. The ratio is increased in advanced cases of massive fibrosis but this is principally due to a fall in the vital capacity, for the absolute value of the residual capacity is, on the average, smaller than in normal subjects. This change is in marked contrast to that found in non-industrial emphysema, when there is usually an absolute increase of the residual capacity with the lung volume remaining normal or being only slightly reduced. Thus to accept residual capacity % T.L.C. as a measure of emphysema without consideration of the age of the subject or the cause of the altered ratio may be misleading.

Another test which has been considered to be an important index of emphysema is the inequality of distribution of air entering the lungs. Many methods for measuring the inequality have been devised. The results depend on such variables as the size of the functional residual capacity and the tidal volume and are affected seriously by the particular method used. Bates and Christie (1950) have recently published a method using a closed circuit helium apparatus. They obtained good separation of normal subjects from a group of advanced cases of emphysema. We have used the same method but failed to obtain nearly as good separation of normal subjects from a group of advanced cases of emphysema. This may be partly due to differences between their apparatus and ours, although these were very small. It may also have been due to our normal subjects being less highly selected. They were men who were attending the local Labour Exchange, and who were employed in our department for a day, their work being to collaborate in a number of pulmonary function tests. Bates and Christie's subjects were, on the other hand, selected as being indubitably free from any chest complaint. On these same groups of subjects our colleague, Dr. Hugh-Jones, measured the inequality of mixing by an open circuit method and expressed the results in rather a different way, which estimates the residual inequality of mixing after allowing for the presence of a series dead space. This index gave much better separation of the normal from the emphysematous subjects. The importance of method has also been emphasized by Comroe and Fowler (1951). They showed that the index of inequality derived from the nitrogen concentration in the alveolar air after a seven-minute period of oxygen breathing is much less sensitive for separating normal subjects from those with emphysema than their own method of measuring the change of concentration of nitrogen in a single expiration by means of the Lilly nitrogen analyser, and they also observed that many other respiratory diseases show abnormality on this test. It is clear that disturbance of intra-pulmonary mixing is but one method of exploring the function of the lungs and cannot be regarded as specific for emphysema.

It seems to us that no single test will ever be specific of this condition, for there are probably many types of emphysema, each with its own grouping of functional disturbance. Thus, in one type there may be relatively severe disturbance of intra-pulmonary mixing with a small change in R.C.% T.L.C., while in another the exact converse may be true. These types may, of course, have their counterparts in the pathological varieties shown by Professor Gough.

We think the best way of using physiological methods for the diagnosis of emphysema is to employ several tests. For example, if Tests A and B both separate normal subjects from those with emphysema to some degree, a combination of the two tests may well separate the two better. In employing this method we are following that used by the clinician. From his experience he assesses the probability of emphysema by giving due weight to the signs, symptoms and history. The physiologist can do the same, but has the advantage of having measurable indices and an objective method of weighting. His difficulty has been in the method of presenting the results. It is here that the statistical technique of discriminant analysis, developed by Fisher (1936), is of particular value. The method provides a single index which maximizes the difference between any two groups of results in relation to the scatter within them. The index takes the form of the sum of particular multiples of the test results:

$$f = a \times (\text{Test 1}) + b \times (\text{Test 2}) - c \times (\text{Test 3}) + d \times (\text{Test 4}) \text{ etc.}$$

For the selection of the tests and calculation of the multiples it is desirable to compare a reasonably large group of normal subjects with a group of subjects of comparable age with advanced emphysema, using all tests which are likely to be relevant to the various aspects of emphysema.

So far we have only been able to compare a small group of 10 normal subjects aged 55 with a group of 5 cases of moderate and advanced non-industrial emphysema (average age 54). These five cases had been observed over a number of years in Professor Christie's Department, and showed a majority of the clinical and physiological features described in the literature as associated with emphysema. The comparison was made on eight tests which are listed in order of their sensitivity in separating the two groups:

1. Intra-pulmonary Gas Mixing (Open Circuit Index).
2. Maximum Breathing Capacity.
3. Residual Capacity % T.L.C.
4. Functional Residual Capacity.
5. Diaphragmatic Movement.
6. Vital Capacity.
7. Diaphragm Level.
8. Carbon Monoxide Uptake.

Various combinations of these tests were tried and the best discrimination of the normal group from the men with emphysema was obtained by one including the first four on the list. The function so derived was then calculated for groups of normal subjects, and of miners with simple and complicated pneumoconiosis. Each group was balanced for age and contained the same proportion of men aged 35 (± 2), 45 (± 2) and 55 (± 2). The discriminant function gave a small scatter with age in each group, and good separation of the normal subjects from miners with Category D complicated pneumoconiosis who thus had good evidence of emphysema as judged by this combination of tests. By contrast, the R.C.% T.L.C. showed a wider scatter in each group which was related to age and less clear separation of one radiological group than another, so that judged on this single test it was not possible to be certain that men with Category D had emphysema. A similar wide scatter within the groups, and poor separation, was observed using a clinical assessment of emphysema based on the seven physical signs—Fixity of chest, Shape of chest, Impairment of cardiac dullness, Impairment of liver dullness, Hyper-resonance, Epigastric pulsation, Diminished breath sounds—each of which was given equal weighting.

In conclusion, we think that a single physiological index is an unsatisfactory method of assessing emphysema, and in its place we suggest a combination of several tests, combined in the form of a discriminant function. The method provides better separation of the normal from the abnormal and uses, most efficiently, all the physiological information available. Large groups and a wide selection of tests should permit the establishment of a satisfactory and sensitive index which could be used to assess, objectively and repeatably, the degree of emphysema in an individual or a community.

A fuller account of this work, and a consideration of the advantages and limitations of discriminant analysis for this purpose, will be published elsewhere.

We wish to acknowledge our indebtedness to Professor R. V. Christie and the subjects who made this comparison possible.

(This communication was illustrated by slides.)

REFERENCES

BALDWIN, E. DE F., COURNAND, A., and RICHARDS, D. W. (1949) *Medicine, Baltimore*, **28**, 201.

BATES, D. V., and CHRISTIE, R. V. (1950) *Clin. Sci.*, **9**, 17.

COMROE, J. H., and FOWLER, W. S. (1951) *Amer. J. Med.*, **10**, 408.

FISHER, R. A. (1936) *Ann. Eugen., Camb.*, **7**, 179.

GREIFENSTEIN, F. E., KING, R. M., LATCH, S. S., and COMROE, J. H. (1952) *J. appl. Physiol.*, **4**, 641.

MCCANN, W. S. (1939) Proc. 4th Saranac Laboratory Symposium on Silicosis, Saranac Lake, N.Y., 1939, p. 93.

MOTLEY, H. L., LANG, L. P., and GORDON, B. (1949) *Amer. Rev. Tuberc.*, **59**, 270.

JOINT MEETING No. 5

Section of Endocrinology with Section of Pædiatrics

Chairman—A. W. SPENCE, M.D., F.R.C.P.
(President of the Section of Endocrinology)

[*April* 23, 1952]

Adrenogenital Syndrome with Insufficiency of the Electrolyte-regulating Function of the Adrenal Cortex.—S. A. DOXIADIS, M.D. (by permission of Professor R. S. ILLINGWORTH, M.D., F.R.C.P.).

C. S., born January 31, 1949. Birth weight 3,150 grammes. Second child. The first died in the neonatal period having some malformation of the genitalia. Information about the cause of death is lacking. The present patient began to vomit occasionally at the age of 1 week. The vomiting became persistent and projectile at the age of 3 weeks. The vomiting continued till the age of 8 weeks when the infant was admitted, severely dehydrated and having lost 450 grammes since birth, to the Children's Hospital, Sheffield. The provisional diagnosis of pyloric stenosis was not confirmed at subsequent examinations. The infant had a severe degree of "hypospadias" (Fig. 1). The serum sodium was low

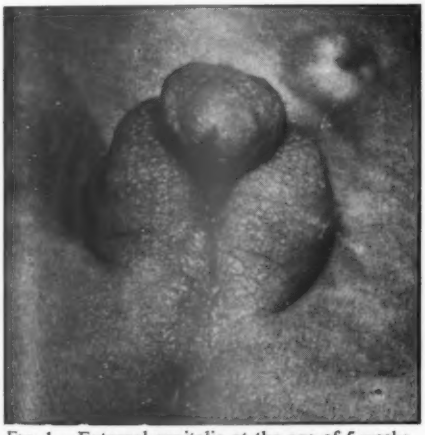

FIG. 1.—External genitalia at the age of 5 weeks.

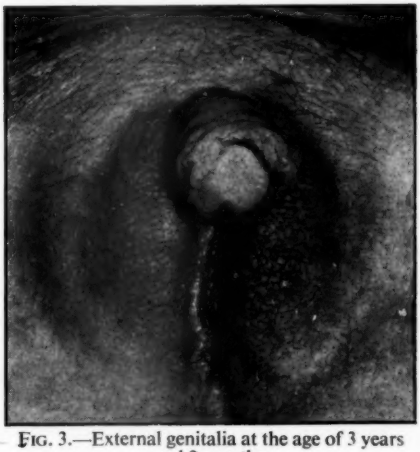

FIG. 3.—External genitalia at the age of 3 years and 2 months.

(290 mg./100 ml.) while sodium was excreted in the urine in normal quantities. This biochemical pattern suggested deficiency of the electrolyte-regulating hormone of the adrenal cortex. The response of the serum sodium and of the weight to administration of D.C.A. and of Eucortone is shown in Fig. 2. An attempt to discontinue treatment at the age of 8 months failed, the serum sodium falling to the very low level of 240 mg. per 100 ml., but a second attempt at the age of 14 months was successful and the infant has not received any more D.C.A. or Eucortone since then.

The presence of a disturbance of the electrolyte-regulating function of the adrenal cortex suggested that other functions of this gland might also be disturbed and that the diagnosis of hypospadias might have to be altered to female pseudohermaphroditism. This possibility became more likely when at the age of 18 months the amount of 17-ketosteroids excreted in twenty-four hours' urine was found to be 6 mg. Final confirmation was obtained at the age of 2 years. Explorative laparotomy revealed normal uterus, tubes and ovaries. At the same time the perineal sinus was incised backwards (Mr. R. Zachary). Fig. 3 shows the external genitalia at the age of 3 years and 2 months. At this age the bone age is very advanced, corresponding to that of a child of 9 years. The child is now being brought up as a girl.

Numerous cases of the adrenogenital syndrome leading to macrogenitosomia in the male and pseudohermaphroditism in the female have been reported, but the combination of adrenogenital syndrome with an impairment of the electrolyte-regulating function of the adrenal cortex is much less common and many of the children described died early in infancy. Others at the time of reporting were still in infancy.

I have only been able to find 7 cases in the literature who at the time of reporting were over 1 year of age. 2 were males, one (Butler *et al.*, 1939; Gardner *et al.*, 1950) 11 years old and the other (Knudson, 1951; Case 11) 21 months old, and both still required treatment with D.C.A. 5 were females and 4 of them (Panos, 1950; Hinman, 1951: Cases 1 and 2) still required treatment with D.C.A. at the age of 16, 17, 42 and 42 months. In one of the females (Knudson, 1951: Case 8) treatment with D.C.A. had been discontinued at the time of reporting when the infant was 21 months old and the subsequent course is therefore not known.

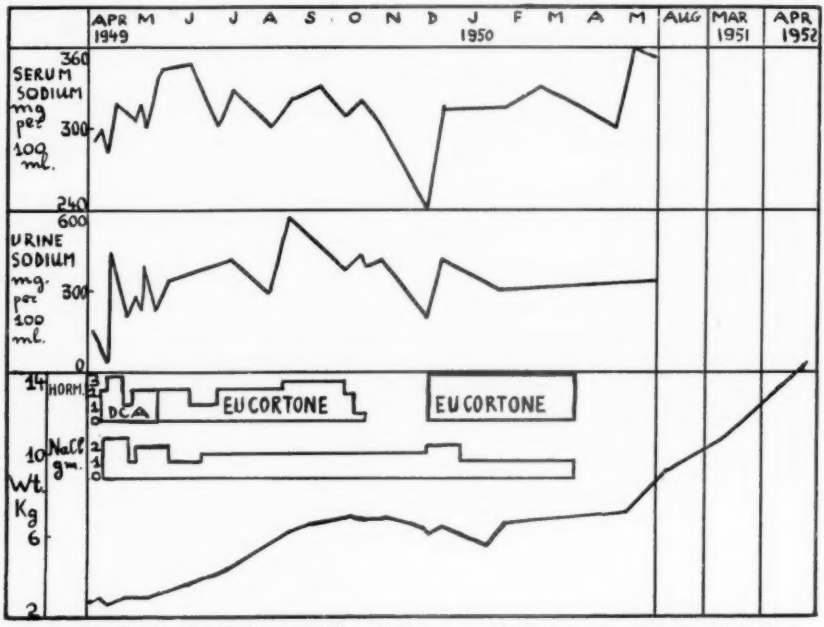

FIG. 2.—Biochemical findings, weight and treatment. (D.C.A. in mg. Eucortone in ml.)

The present case demonstrates that it is possible for a patient with the adrenogenital syndrome and insufficiency of the hormones regulating the electrolyte metabolism, not only to survive the Addisonian crises if adequately treated, but also to recover completely both clinically and biochemically from this insufficiency. The adrenogenital syndrome of this patient due to an excess secretion of androgens is, however, more permanent and it has already caused pseudohermaphroditism and very advanced bone age.

It has been suggested (Hinman, 1951), that since in cases of this type the androgenic stimulation will continue for the rest of their lives, it may be wiser to allow them to grow up as males. Recent reports, however, on the suppression of the excessive androgenic activity by the administration of cortisone (Wilkins *et al.*, 1950; Wilkins, 1952) offer the hope that the progressive masculinization may be interrupted and that the female patients will be able to develop physiologically.

REFERENCES

BUTLER, A. M., ROSS, R. A., and TALBOT, N. B. (1939) *J. Pediat.*, **15**, 831.
GARDNER, L. I., SNIFFEN, R. C., ZYGMUNTOWICZ, A. S., and TALBOT, N. B. (1950) *Pediatrics*, **5**, 808.
HINMAN, F., Jr. (1951) *J. Amer. med. Ass.*, **146**, 423.
KNUDSON, A. G. (1951) *J. Pediat.*, **39**, 408.
PANOS, T. C. (1950) *Pediatrics*, **5**, 972.
WILKINS, L. (1952) *Pediatrics*, **9**, 338.
——, LEWIS, R. A., KLEIN, R., and ROSENBERG, E. (1950) *Bull. Johns Hopk. Hosp.*, **86**, 249.

Dwarfism, Microcephaly and Splenomegaly.—KEITH LOVEL, B.M., M.R.C.P. (for G. H. NEWNS, M.D., F.R.C.P.).

S. H., girl aged 15 years.

First attended The Hospital for Sick Children at age of 10 years on account of smallness and backwardness. Parents had not regarded her as being unduly short until she was 8, but when in another hospital at age of 2 she was described as "very undersized". Said her first words at $1\frac{1}{2}$, and walked at $2\frac{1}{2}$ years; had always been constipated and felt the cold easily.

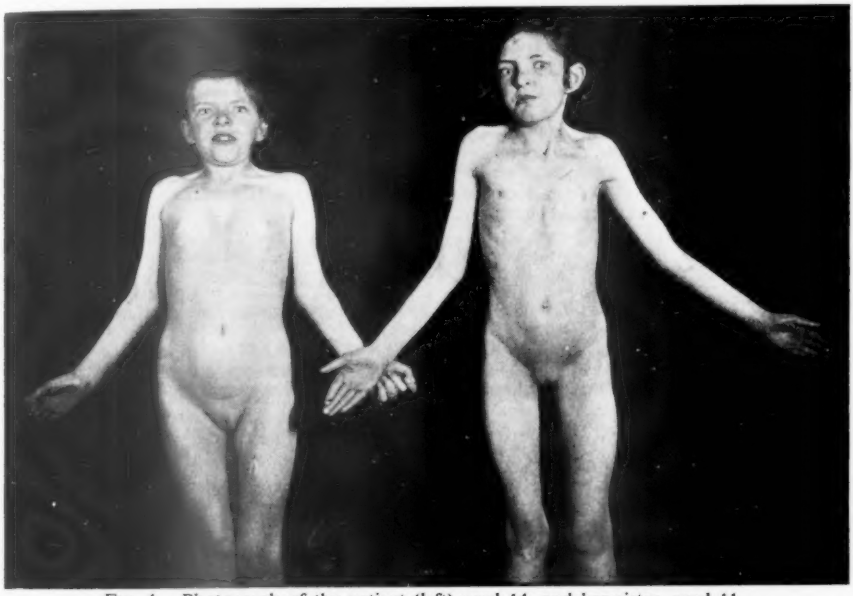

FIG. 1.—Photograph of the patient (left) aged 14, and her sister, aged 11.

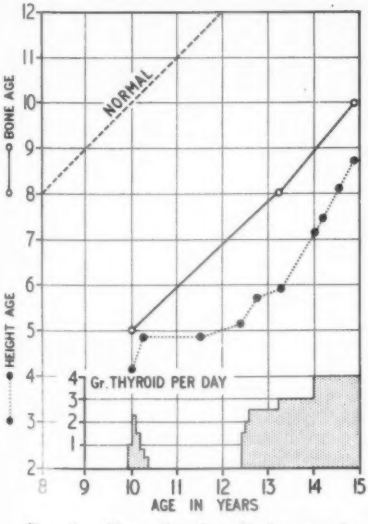

FIG. 2.—Chart showing the increase in bone age and "height age", with thyroid treatment. (*After* Wilkins.)

Family history.—Mother also short (60 in.): did not menstruate until 18 and has always had scanty pubic and axillary hair. ? webbing of neck. 1 sister, aged 11, height 51 in. 1 brother, aged 6, has six toes on one foot. No consanguinity.

On examination (28.2.47).—Height $40\frac{1}{2}$ in. (normal 51–55 in.). Weight 42 lb. (normal 56–71 lb.). Head circumference $18\frac{1}{2}$ in. (normal $20\frac{1}{2}$ in.). High myopia. Rather widely spaced eyes with persistence of epicanthic folds. Slight webbing of neck and cubitus valgus (Fig. 1). No goitre. Dry scaly skin. Hands blue and cold. Funnel depression of sternum and genu valgum. Heart and lungs normal. Pulse-rate 100/min. B.P. 110/65. Abdomen: spleen enlarged 2 f.b., liver enlarged 1 f.b.

X-ray investigations. (Dr. G. N. Weber)—Wrist and elbow: bone age is retarded (approximately 5 years in 1947). Skull: Abnormally small, and orbits set widely apart. Pituitary fossa rather large. Dorsum sellæ small. Spine: Several bodies of dorsal vertebræ rather poorly formed.

ECG (Dr. R. E. Bonham Carter): "Bradycardia: the lowest voltage I have ever seen."

Blood cholesterol 210 mg./100 ml. Blood W.R. and Kahn negative. Insulin tolerance test (5 units subcutaneously): Time 0 20 40 60 100 min.
Blood sugar 92 92 79 85 94 mg./100 ml.
Urine: No sugar or albumin. Follicle-stimulating hormone (Dr. G. I. M. Swyer, 31.7.50): less than 5 mouse units per twenty-four hours.
Intelligence quotient 65.

Treatment and progress.—Was started on thyroid, and is now having 4 grains daily. She has grown 9½ in. but has only gained 12 lb. She still feels the cold, but is no longer constipated and is normally active. Still very backward at school, and childish in attitude and behaviour. No signs of puberty have appeared. Bone age now 10 years (Fig. 2); blood cholesterol 180 mg./100 ml. ECG has become normal and B.M.R. in May 1951 was +5%.

The Chairman said that both the webbing and the cubitus valgus were of sufficient degree to warrant the diagnosis of ovarian agenesis.

In reply to a question, **Dr. G. I. M. Swyer** said the F.S.H. estimation at the age of 13 could not altogether exclude ovarian agenesis, and it should be repeated again now.

Dr. Russell Fraser said the child had not been proved to be hypothyroid, and that a similar amount of growth could be produced by thyroid treatment in other types of dwarfism. He thought it would be worth studying the metabolism of radio-active iodine in this case, and observing the effect of thyrotrophic hormone. The possibility of a lipoidosis might also be investigated by bone-marrow biopsy and splenic puncture.

Dr. Alex Russell commented on the family history. When Dr. Lovel kindly arranged that he saw the family, he recognised within it a unique trio, namely a mother showing evidence of some form of ovarian hypoplasia, or delayed initiation of gonadotrophic stimulation, sharing with her two daughters other basic criteria of Turner's syndrome,

In reply **Dr. Lovel** agreed that there were many features not typical of hypothyroidism, and that this could not be the sole diagnosis, but said that the clinical findings of cold extremities, sluggishness and constipation, together with the ECG, seemed to indicate thyroid treatment, which he thought had been justified by the response.

POSTSCRIPT (August 1952).—The urinary F.S.H. estimation was repeated by Dr. Swyer and again gave a result of less than 5 mouse units in twenty-four hours. Radioactive iodine studies kindly undertaken by Dr. Russell Fraser confirmed the existence of thyroid deficiency.—K.L.

Isosexual Precocity.—DUNCAN LEYS, M.D., F.R.C.P.

Isosexual precocity is said to be much more common in girls than in boys. Most pædiatricians will have seen one or two cases and I imagine that endocrinologists see rather more. Novak (1944) has been especially concerned to identify the benign or constitutional type, which is almost confined to girls, although a few male cases have been reported (Lawson Wilkins, 1948; Engstrom and Munson, 1951).

All are now agreed that cases of isosexual precocity can be divided roughly as follows (both sexes):

(1) Idiopathic or constitutional (80 to 90%).

(2) Gross hypothalamic lesion (less than 10%).

(3) The remaining 5 to 10% have been associated with a variety of lesions, namely: Granulosa-cell tumour of ovary. Interstitial cell tumour of testis. Fibrous dysplasia of Albright (genetic linkage). Dysgerminoma of ovary. Tumour of adrenal cortex. Teratoma.

In brief, the last heterogeneous group are distinguished either by obvious collateral signs, as in the bone disease and pigmentation of fibrous dysplasia, or by the presence of a tumour, obvious on first examination or determined without much difficulty by investigation.

Of the second group, making up about 10% of the whole, there were only about 20 reported by 1947, and these were, oddly enough, nearly all boys. The majority appeared to have followed some form of encephalitis, but a variety of local lesions have caused this syndrome, such as basal tuberculous or syphilitic meningitis, hydrocephalus, developmental defects of the brain associated with mental retardation, and (very rarely) tumour. Notably, it has not been reported as associated with disease of the pituitary itself. Most of these cases have had a high output of ketosteroids. The most precise definition of a local lesion has been in the mammillary nuclei of the hypothalamus, but all have been of a kind to involve this structure, either by pressure or by destructive or degenerative process.

The patient is a girl of 4 years of age. She is not a case of the rare granulosa-cell tumour, nor of fibrous dysplasia. Ketosteroid excretion is not increased. Urinary pregnandiol is of the order of 9 mg. per day. The Aschheim-Zondek test is negative.

She is a restless child, inclined to outbursts of temper, and examination is difficult. She shows advanced growth in stature and ossification, moderate enlargement of nipples and breasts, some pubic, but no axillary hair, slight vaginal discharge but no bleeding. Her height at 4½ years is 47 in., well outside the normal range and about 5 in. above the average. She has grown more than 4 in. in the last twelve months. Her epiphyseal development is that of a child of 8 to 10 years. There is slight seborrhœa of the face. Dentition is normal for her age, i.e. lags behind her skeletal growth. Examination under anæsthesia (Mr. Rufus Thomas) showed no evidence of a tumour; the uterus was larger than normal. The Wassermann reaction is negative, spinal fluid and blood chemistry normal.

Vaginal discharge was noted at about 6 months of age, and breast enlargement at 12 months. When she was 4 months old, momentary attacks were seen with apparent loss of consciousness. These have continued with variable frequency, diminishing in her 3rd and 4th years, and recently rather more frequent (4 or 5 attacks in twenty-four hours). Their frequency has not been influenced by Tridione or Epanutin. Her mother considers that her behaviour progress was normal until the age of 6 months, and retarded after this. She consulted a specialist on this account when the child was a year old. Her physical progress was uninterrupted. She had sphincter control at the age of 3, and her speech development has been slow. She also had attacks of breath holding. A sister born in 1950 is normal.

The differential diagnosis is considered to lie between so-called constitutional precocity and a hypothalamic pathology. Her sex and the normal ketosteroid output are in favour of the benign type, her epilepsy and mental retardation (I.Q. = 71) suggest a brain lesion. There are no focal signs of brain disease, however, and the X-ray of skull is considered normal. The EEG (Dr. D. A. Pond, Maudsley Hospital) shows a number of slow spike and wave complexes which are bilaterally synchronous and symmetrical, and tend to be precipitated by eye closure and blocked by eye opening. The fast and slow activity present in the record are doubtfully in excess for the age. Photic stimulation produced little change in the record.

It seems quite possible that some form of encephalitis did occur in the early months, with sequential epilepsy, mental retardation and sexual precocity. A decision as to whether this child has in fact a structural lesion of the hypothalamus is not of great importance as regards treatment, since it seems clear that, if present, it forms part of some more widespread pathology. The prognosis would of course be affected to some degree.

The expectation in the constitutional type is of sexual development which can be regarded as normal but premature. Patients who have been followed through, or known in adult life from case histories, have established normal ovular menstruation: many have married and have borne children, and one woman, menstruating at the age of 2, had her menopause at 50. The earliest pregnancy on record is of a girl of 5, whose pregnancy went to term and was ended by Cæsarean section.

The constitutional cases are probably genetic. There are several families on record with precocious sex development in consecutive generations; curiously enough, many of these records are of males, but there is no doubt about its familial occurrence in both sexes.

Transient premature sex development has been noted on several occasions, and I have myself seen a girl of 4 years, who developed breast enlargement and vaginal discharge, both of which disappeared in the course of a few months, to be followed by a single scanty uterine hæmorrhage. In some cases, a partial or tentative development occurs, and persists as a solitary phenomenon for some years. Lawson Wilkins (1948), for example, has described the appearance of pubic hair followed by normal puberty at 9 or 10 years of age. An interesting case is on record of transient breast enlargement apparently due to the inhalation of dust from the packing of stilbœstrol tablets by the girl's mother as a home industry.

The initiation of normal puberty is believed to occur as the result of the production of trophic factors by the pituitary. The stimulus to the pituitary is presumably neurogenic, and the result of the total maturation of the individual. There are, of course, both ethnic and climatic differences in the time of its appearance, so that both genetic and environmental factors are involved. Most cases of progressive isosexual precocity are presumably genetic, and the transient cases environmental, resembling the common transitory growth stimulus to the infant's breasts.

The cause of the excessive growth of the skeleton is not entirely obvious. It is possible that there is a secondary stimulus to the pituitary as a result of the production of follicular hormone, causing an increased output of growth hormone. Œstrogen itself appears to have little anabolic effect, but does tend to cause early maturation and closure of the epiphyses, which probably accounts for the small adult stature of these patients; that this is not the whole story, however, is shown by the fact that girls with ovarian agenesis are of short stature, and that castrates cease growth in height with open epiphyses.

REFERENCES

ENGSTROM, W. W., and MUNSON, P. L. (1951) *Amer. J. Dis. Child.*, **81**, 179.
WILKINS, L. (1948) *Advanc. Pædiat.*, **3**, 159.
NOVAK, E. (1944) *Amer. J. Obstet. Gynec.*, **47**, 20.

Diabetic Infantilism with Diabetic Nephropathy.—G. C. MANNING, M.A., M.B., B.Chir.

J. K., male, Irish, aged 18, was admitted to West Middlesex Hospital on October 2, 1951, with two months' history of loss of energy, blurring of vision, and occasional headaches. Swelling of the ankles, first noticed eighteen months previously, had increased recently. He had come to England in April 1951, since when he had been employed as a bell-boy in a large hotel.

Past history.—He admitted that he had suffered from undue thirst since about 1944, and that for as long as he could recall he had had polyuria with nocturnal frequency. As a child he had frequent enuresis. His general health remained good until in November 1946 he was admitted to another hospital in coma. This had followed a twenty-four-hour illness consisting of vomiting, pain in the abdomen, and increasing drowsiness. Coma responded to repeated injections of insulin and for the next six months he continued to have insulin injections at home. Treatment brought symptomatic relief particularly from thirst, but was discontinued by the patient. Since the end of 1947 polyuria and thirst have returned. Growth apparently ceased at the age of 12 and body-hair had never developed.

Family history.—There is no family history of diabetes. He has 3 brothers; one aged 10 is smaller and the others aged 13 and 20 respectively are taller than the patient. The father is tall (6 ft. 2 in.).

On examination (22.10.51).—Cheerful, intelligent, undersized, normally proportioned male, afebrile, weight 76 lb., height 4 ft. 7 in., with pale, dry and rather powdery skin. Abdomen rather protuberant with wide subcostal margin (Fig. 1). Genitalia infantile—with hypoplastic penis and bean-sized testicles at the external inguinal orifices (Fig. 2). Absent pubic, axillary and facial hair. Slight œdema

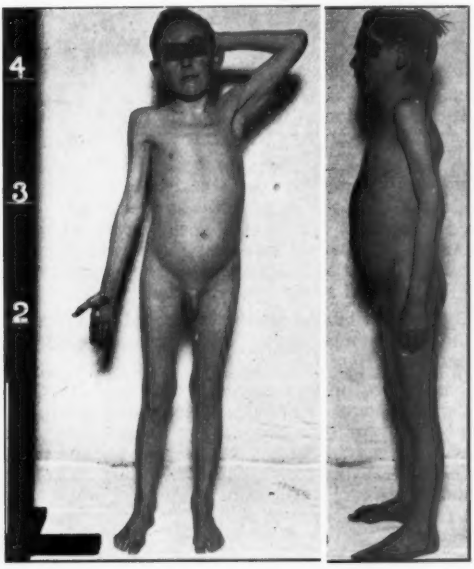

FIG. 2.—Diabetic infantilism. Patient aged 17½ years.

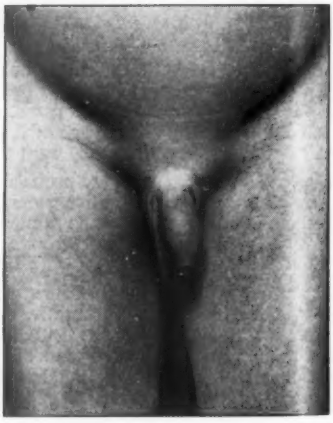

FIG. 2.—Infantile genitalia. (Aged 17½ years.)

of the ankles and sacrum. Thyroid isthmus palpable. No lymphadenopathy. No clubbing. The nails of the thumbs show some thickening and are white with pink lunules. Voice high-pitched.

C.V.S.: *Pulses* equal. Vol. smallish. Regular. Rate 100. B.P. 135/100. *Heart.* Apex 5th i.c.s. 3 in. to L. of M.L. Soft apical systolic bruit. J.V.P. normal. Lungs: Occasional fine rhonchi at both apices. Abdomen: Enlarged liver—3 f.b. below subcostal margin on full inspiration, non-tender, with a regular sharp inferior margin. Spleen not palpable. C.N.S.: Reflexes present and equal except ankle-jerks which are absent. Plantars flexor. No sensory loss. Fundi: Widespread clusters of small hard, yellow-white exudates with occasional small hæmorrhages near the vessels and micro-aneurysms. Veins congested. Slight blurring of the nasal margins of the discs.

Investigations (pre-therapeutic).—Urine: Daily urine volume (prior to insulin) ranged from 110–200 oz., with intakes ranging from 70–100 oz. Output always higher than fluid intake. Sp. gr. 1020. Acid reaction. Albuminuria constant (9·02 grammes/twenty-four hours). Glycosuria (113·9 grammes/twenty-four hours). Rothera and Gerhardt tests negative. R.B.C. and epithelial cells occasionally present. Culture yielded moderate growth *B. coli.* 19.10.51: Casts nil.

Blood: Hb 94% (13·9 grammes). W.B.C. 7,100. Polymorphs. 52, lymphos. 42·5, monos. 4, eosinos. 1·5%.

E.S.R. 65 mm. in the first hour (Westergren).

W.R., Kahn negative.

Urinary 17-ketosteroids 5·8 and 4·6 mg. (as neut. androsterone)/twenty-four hours on two examinations.

Blood chemistry: Fasting blood sugars 301, 520, 298, 304 mg.%. Urea 40 mg.%. Total proteins 5·4; alb. 2·3, glob. 3·1 grammes %.

Sodium 305, potassium 16·8, calcium 10·2, inorg. phosphorus 4·3 mg.%. Alkali reserve 53 vol. CO_2%. Alkaline phosphatase 11·8 K.A. units. Thymol turbidity 3 units. Thymol flocculation negative. Serum colloidal gold negative. Bilirubin 0·5 mg.%.

Glucose tolerance test: Diabetic curve—insulin sensitive (Fig. 3). Urea clearances 51% and 60% max. Urinary excretion of I^{131} normal. B.M.R. plus 8%. E.C.G. Sinus tachycardia. Normal voltage.

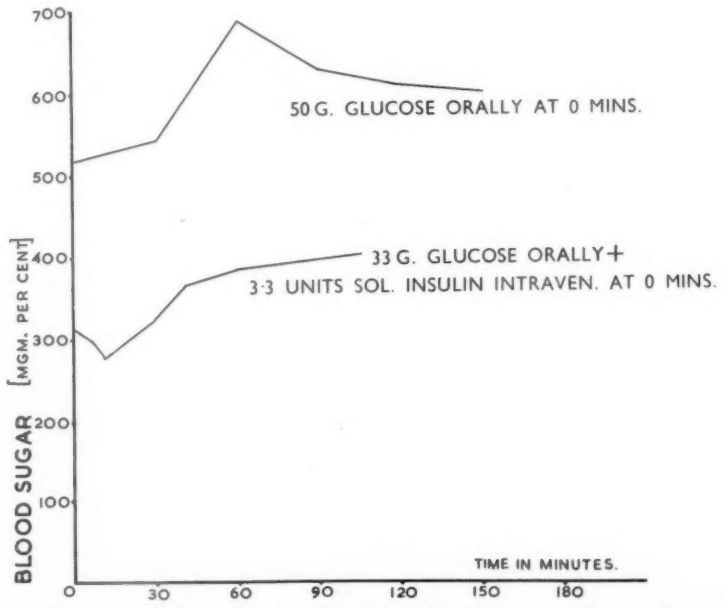

FIG. 3.—Diabetic infantilism. Blood sugar curves on first admission, to show insulin-sensitive diabetes mellitus.

X-rays: Sella turcica 0·9 × 0·65 cm. (lat. radiograph). Posterior calcanean and upper radial epiphyses ununited. Epiphyses of humerus and distal end of tibia and fibula ununited.

Progress.—Insulin therapy commenced. S.I. 5 units b.d. on 10.11.51 with 2,000 calories (180 grammes carbohydrate) diet daily. Urine output fell after forty-eight hours, and thirst was correspondingly reduced. Insulin and diet subsequently increased with reduction in hepatomegaly and of glycosuria. General condition has, however, deteriorated with increase in retinopathy, including macular œdema and fresh hæmorrhages and the onset of burning and tingling paræsthesiæ in both legs. Peripheral œdema has varied in degree extending in January 1952 to involve the face, hands, sacrum and legs with evidence of pulmonary œdema and early left ventricular failure. B.P. generally 130/105 and rising occasionally to 190/105 and 160/115. Glycosuria and proteinuria have varied under treatment within wide limits, up to 124 grammes glucose and 15·5 grammes albumin per twenty-four hours, with a spontaneous creatinuria of 73–300 mg./twenty-four hours and creatininuria from 927–1173 mg./twenty-four hours. Blood cholesterol in February 475 mg.%.

Severe hypoglycæmic coma necessitated readmission in February 1952. Coma responded immediately to I.V. glucose administration. Control has since been maintained on 20 units PZI. and 20 units S.I. omni mane, with 2,500 cal. (250 grammes carbohydrate) diet. Present weight 81 lb. Height 55¾ in.

Comments.—J. K. exhibits the clinical features of diabetic infantilism with the triad of hypertension, proteinuria, and retinopathy. The latter syndrome together with peripheral neuropathy and œdema have been related (Gilliland, 1951) to the changes of intercapillary glomerulosclerosis in the kidneys, described by Kimmelstiel and Wilson (1936).

Renal damage has been regarded (Joslin and Wilson, 1950) as the commonest cause of death in young patients with diabetes commencing under the age of 15 years, though clinical evidence of renal complications has appeared earlier in this case than is perhaps usual. Wilson *et al.* (1951) found that such evidence was commonest in patients in the 4th and 5th decades who had had severe, poorly controlled diabetes for twenty years or more. They noted signs of diabetic nephropathy in 25% of a group of 247 young patients with severe diabetes of ten to thirty-four years' duration, and further that no patient who had enjoyed excellent control exhibited evidence of renal damage even after diabetes had been present for twenty to thirty-four years. In this series, death occurred about eleven years after the first manifestations of nephropathy. The same workers showed that histological changes of acute and chronic pyelonephritis and arteriolosclerosis invariably co-exist with intercapillary glomerulosclerosis in affected kidneys. Urine cultures in this case yielded *B. coli* on first admission and *Strep. fæcalis* subsequently.

The relative absence of ketosis and the small insulin requirements in this case are interesting. Zubrod *et al.* (1951) pointed out that in cases showing Kimmelstiel-Wilson lesions at necropsy, the disease was characterized by a progressive fall in insulin need and a tendency to hypoglycæmia on small doses. Failure to develop ketosis was also a feature.

Referring to the retinal changes, Friedenwald (1950) noted that retinopathy with capillary aneurysm formation is seen in younger diabetics since the insulin era, though usually not for ten to fifteen years after the onset of diabetes, and suggested that the retinal changes and intercapillary glomerulosclerosis were manifestations of the same process.

With regard to the association of infantilism and diabetes, Gibson and Fowler (1936) describe 8 such cases in which, diabetes had either not appeared or was adequately controlled at the age of puberty. Malnutrition was not evident and it was suggested that hypofunction of the anterior pituitary was responsible for the physical characteristics. In this case, however, the absence of adequate control until recently makes it probable that infantilism has resulted from chronic metabolic disorder and the diversion of materials necessary for normal development.

REFERENCES

FRIEDENWALD, J. S. (1950) *Amer. J. Ophthal.*, **33**, 1187.
GIBSON, R. B., and FOWLER, W. M. (1936) *Arch. intern. Med.*, **57**, 695.
GILLILAND, I. C. (1951) *Brit. med. J.* (i), 916.
JOSLIN, E. P., and WILSON, J. L. (1950) *Brit. med. J.* (ii), 1293.
KIMMELSTIEL, P., and WILSON, C. (1936) *Amer. J. Path.*, **12**, 83.
WILSON, J. L., ROOT, H. F., and MARBLE, A. (1951) *New Engl. J. Med.*, **245**, 513.
ZUBROD, C. G., EVERSOLE, S. L., and DANA, G. W. (1951) *New Engl. J. Med.*, **245**, 518.

Chondrolipodystrophy (Gargoylism).—I. C. GILLILAND, M.D., M.R.C.P.

A. M., aged 17 years.

History.—Weighed 7 lb. at birth. Appeared normal. Walked at 11 months. Talked at 18 months (Fig. 1). Slight limp at 2½ years and was then diagnosed as having rickets.

School at age of 5. Noted to have large liver and spleen when aged 6 and tentative diagnosis of gargoylism made. Did reasonably well at school, cycling there and back. Now learning shorthand and typing.

Family.—No known cases on either side of parents. One sister normal.

Clinical examination.—Dwarfed 3 ft. 11½ ins. Skull fairly proportionate to size, hair silky. Features heavy, coarse eyebrows, thick eyelids and protuberant eyes. Bridge of nose depressed and alæ thickened. Lips coarse and thickened, tongue enlarged. Stridor on exertion or excitement. Corneæ clear. Optic fundi show gross papillœdema. Bilateral partial nerve deafness.

Lumbar kyphosis and protuberant abdomen with umbilical hernia. Liver and spleen enlarged and soft and smooth. Puberty under way. Genitalia adolescent and some pubic hair present.

B.P. 150/100. Urine N.A.D. Extension of all joints and of the extremities limited most severely, there being practically no movement in fixed, flexed terminal phalanges of both hands and feet. Extremities rather cold and blue and skin dry. Mental development sufficient to make him practise typing assiduously and be anxious to earn his own living.

X-ray findings.—Skull: Large skull for age of patient, with slight springing of the suture. The pituitary fossa is deepened and there is undercutting of the anterior clinoids. The base of the skull is rather short and slightly invaginated—platybasia (Fig. 2). Optic foramina are comparable in size and there is no evidence of local bone change. Teeth are fully developed and of excellent shape. Denture suggests a much older patient.

I. C.

FIG. 1.—Aged 18 months.

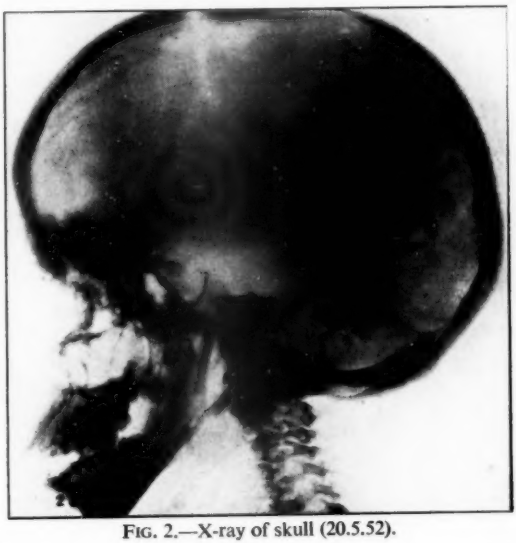

FIG. 2.—X-ray of skull (20.5.52).

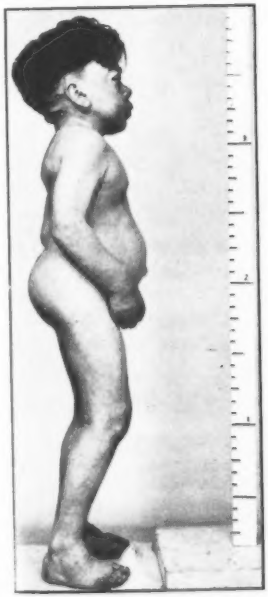

FIG. 4.—Aged 17 years.

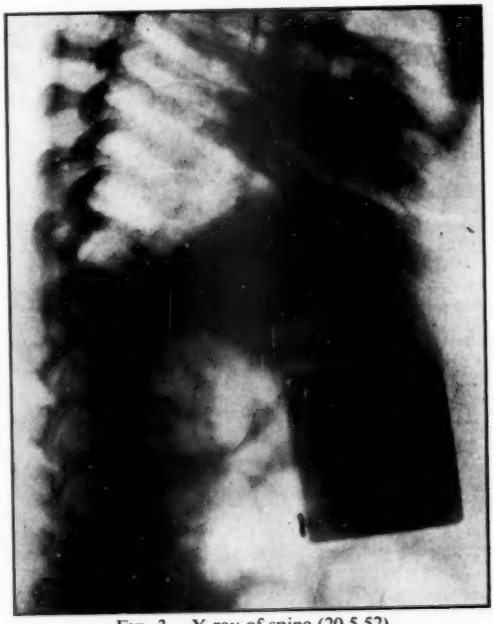

FIG. 3.—X-ray of spine (20.5.52)
Inset.—Normal vertebra as standard.

Dorsal spine: Considerable deformity of vertebral bodies, which are diamond-shaped. Localized osteochondritis between L.2 and 3—they do not seem to be markedly decalcified. Note slender abnormal shape of posterior aspects of ribs (Fig. 3).

Pelvis: Narrowed sacro-iliac joints with beaking of both inferior surfaces. Osteochondrodystrophy of both femoral heads, which are abnormally developed. Short stumpy foramina. Fairly well-developed femoral and tibial epiphyses.

Hands and wrists: Bones of hands and wrists are stumpy and broad. Normal development of carpus which shows delayed ossification but no gross osteoporosis. Considerable deformity of the epiphyses, again due to osteochondrodystrophy. Fingers are short and stumpy with considerable flexion deformity of the terminal phalanges (Fig. 4).

The cold, blue extremities and the findings of Ashby *et al.* (1937) suggested the possibility of hypothyroidism, but this was not confirmed by I^{131} excretion (0–8 hours 31·6%; 8–24 hours 4·1%; 24–48 hours 3·0%. Total 38·7%.)

Progress.—Has been on thyroid extract, 1 grain, daily and dietetic adjustment, including 1 pint milk. Has gained 5 lb. in weight and ¾ in. in height in four months.

Discussion.—The first description of this disease was given by Hunter before this Society in 1917 as a rare disease, occurring in 2 brothers. Cockayne (1936) also showed 2 brothers at this Society and Ellis (1936, 1938) showed several cases and gave the name gargoylism to the condition.

This case is particularly interesting on several accounts. His handicaps are largely those of dwarfism and locomotor disability. Even the deafness, common to this condition, has been thought by Smith *et al.* (1952) to be due to ankylosis of the malleo-incudal joint with secondary change. Quite a few cases have been described of normal mental development, including one who was an outstanding student and a keen chess player (Straus *et al.*, 1947). Those of relatively normal intelligence have usually been amongst those 25% who show no corneal opacities (Cordes and Hogan, 1942). While most cases have been described in children, several even older than this patient have been described, notably two, 18 and 29, by Smith *et al.* (1952).

Dwarfism has probably two aspects. Infiltration of the growing end of the epiphyses by the unknown substance is probably the major disorder. Endocrine glands probably also contribute (Henderson, 1940). No constant change has been observed but most commonly infiltration has been seen in the pituitary and the thyroid, and X-ray of the pituitary fossa often shows the characteristic deformity shown by this case.

The nature of the infiltrating substance was first thought to be lipoid (Ellis *et al.*, 1936; Ashby *et al.*, 1937) especially in the brain, but was not identified. Recently, Lindsay *et al.* (1948) have suggested that it is glycogen or a similar macro-molecular substance and Smith *et al.* (1952) produced detailed histological and chemical proofs that show that the disease does not chiefly involve lipoids.

BIBLIOGRAPHY

Ashby, W. R., Stewart, R. M., and Watkin, J. H. (1937) *Brain*, **60**, 149.
Cockayne, E. A. (1936) *Proc. R. Soc. Med.*, **30**, 104.
Cordes, F. C., and Hogan, M. J. (1942) *Arch. Ophthal.*, **27**, 637.
Ellis, R. W. B. (1936) *Proc. R. Soc. Med.*, **30**, 158.
—— (1938) *Proc. R. Soc. Med.*, **31**, 770.
——, Sheldon, W., and Capon, N. B. (1936) *Quart. J. Med.*, **5**, 119.
Henderson, J. L. (1940) *Arch. Dis. Childh.*, **15**, 201.
Hunter, C. (1917) *Proc. R. Soc. Med.*, **10**, Sect. Dis. Child., 104.
Hurler, G. (1919) *Z. Kinderheilk.*, **24**, 220.
Lindsay, S., Reilly, W. A., Gotham, T. J., and Skahen, R. (1948) *Amer. J. Dis. Child.*, **76**, 239.
Smith, E. B., Hempelmann, T. C., Moore, S., and Barr, D. P. (1952) *Ann. intern. Med.*, **36**, 652.
Straus, R., Merliss, R., and Reiser, R. (1947) *Amer. J. clin. Path.*, **17**, 671.

Congenital Ovarian Aplasia: with Minimal Evidence of Ullrich-Turner Syndrome.—Alex Russell, O.B.E., M.D., M.R.C.P., and G. I. M. Swyer, D.M., M.R.C.P. (for I. Anderson, M.D., M.R.C.P.).

P. B., female, aged 14 years 4 months.

Her height of 52·5 in., 10·5 in. below the 50th percentile level for her age, was equivalent to that of a 9½-year-old girl.

History.—Arrest of growth from the age of 9 to 10 years recognized by parents. No previous abnormality of growth appreciated. Birth-weight 6 lb. 12 oz. Pallor of skin characteristic from early infancy.

Family history.—No consanguinity. Two paternal aunts even smaller than patient. One, recently married at 45 years to a man eight years her junior, was found to be 51·5 in. in height and to have webbing of the neck.

Examination.—Stocky habitus (Fig. 1). No skeletal asymmetry. Dimensions indicated absence of any disproportionate retardation of long limb growth, viz.: Span 51·5 in. (10·5 in less than the average for her age). Lower segment 26·0 in. (5·0 in. less than the average for her age, although appropriate to her height). Bone age showed no retardation except for absence of "pre-puberal indices", viz. first metacarpal sesamoid and the secondary epiphyses of the iliac crest.

Facies normal. No immaturity of nasal bridge or jaw. Head circumference: 21·5 in.

Neck: Minimal webbing of the neck appreciated only in the posterior view (Fig. 2) or upon flexion of the neck (Fig. 3).

Elbows: Carrying-angle increased. Lateral deflection of long axis of ulna from that of humerus 26°. Normal mean 16·2° ± 0·5. (Atkinson and Elftman, 1945.)

Thorax: Typically broad shield-like chest with nipples widely spaced and inverted. Mid-sternal depression together with mammary fat deposition gave false impression of true breast development.

Genitalia: Infantile status. No labia minora. Slight clitoridal hypertrophy. Rectal examination: neither cervix nor uterus palpable.

Hair: Scanty dark perineal hair. Axillary nil. Two large whorls of soft lustrous brown hair overlying interscapular and sacral area have persisted since birth.

Skin: Uniform pallor in absence of anæmia (hæmoglobin 94%).

Systems: No abnormality apart from hypertension. Right arm 150/105. Leg blood pressure correspondingly high, 175/115.

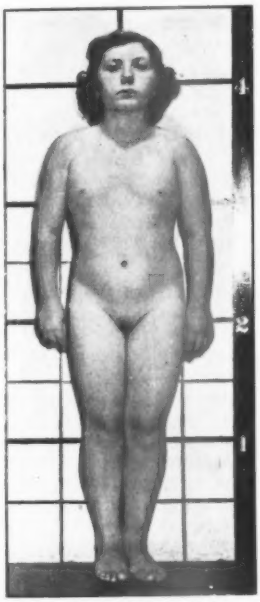

FIG. 1.—Case of congenital ovarian aplasia with features of the Ullrich-Turner syndrome presenting with stunting of growth.

FIG. 2.—Webbing more clearly seen in posterior view of neck.

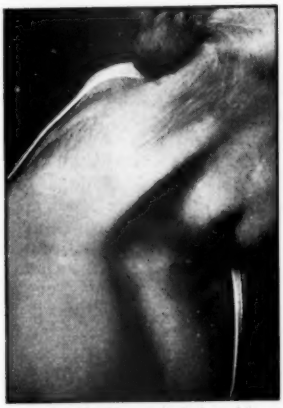

FIG. 3.—Lateral view of right side of neck: webbing displayed by flexion.

Investigations.—Biochemical: Serum sodium 316, potassium 20·5, chlorides 595 mg.%. Serum cholesterol 198 mg.%. Alkaline phosphatase 11·4 K.A. units.

Insulin tolerance test (0·1 unit/kg.): Normal response

Time	0	20	30	45	60	90	120 min.
Blood sugar	70	51	46	58	72	70	73 mg./100 ml.

Radiological: No definite osteoporosis. No maldevelopment of external condyle of humerus to explain cubitus valgus.

Urinary hormone assay (Dr. G. I. M. Swyer, U.C.H.) revealed abnormally high gonadotrophic output linked to abnormally low level of œstrogen fractions: (1) F.S.H.: 160 mouse units/twenty-four hours. (2) Œstrogens: Œstrone nil, œstradiol nil, œstriol 1·7 μg./twenty-four hours. (3) 17-ketosteroids: 6·7 mg.; 11-oxysteroids: 0·43 mg./twenty-four hours (Miss Godsmark, Queen Elizabeth Hospital for Children).

January 1952: *Laparotomy* (Professor W. C. W. Nixon).—Ovaries represented only by a rounded fibrous cord apposed to the broad ligament running below and parallel to the fallopian tubes. Prenatal status of cervix and of uterus which was merely a thickening in the centre of the broad ligament.

Histology of section of rudimentary ovarian tissue.—Normal appearing ovarian stroma with rete ovarii and medullary canals; prominent clumps of "hilus cells" (large, pale-staining polygonal cells, disposed along the course of nerves, and strongly resembling the Leydig cells of the testis). No trace of follicles in any stage of development.

Therapy.—Oral administration of stilbœstrol for past three months, 1 mg. daily for one month, then cyclical administration began with 2 mg. daily for three-week periods, suspending for interval of one week before resuming. Supplement of methyl androstenediol now introduced (10 mg. daily) in endeavour to promote growth without accelerating epiphyseal fusion.

Cyclical administration of œstrogens and progesterone supplemented by methyl testosterone planned at a later stage.

Progress.—Growth: 1¼ in. increment in height in three months. Sexual development: Palpable and visible breast development. First withdrawal bleeding at end of second month of œstrogen therapy. Pubic hair increasing.

Pigmentation: Suntanning evident for first time. Marked areolar pigmentation after two months' therapy.

Comment.—(1) *Cardinal Stigmata*: Evidence of neck webbing, although minimal and only visible posteriorly or upon flexion of the neck, may nevertheless serve to disclose the basic syndrome underlying growth-failure of this type when considered in relation to the wide cubital carrying-angle and infantile sexual development. The presence of neck webbing may well be elicited in like fashion in many cases of ovarian agenesis hitherto recorded as lacking it.

The complete freedom in this case from other multiple congenital anomalies commonly associated, whether they be cardiovascular, musculo-skeletal or ocular, is of interest. It is noteworthy that the raised blood pressure found in this case, as in the majority of typical examples (in a number reflecting aortic coarctation), showed a steady decline from 150/105 to 125/70 during the second month of œstrogen therapy.

(2) *Growth-failure and gonad defect*: Growth in this case conformed with the second of two distinctive patterns of growth-failure found in this syndrome. The first displays a conspicuous smallness from early infancy. In the second an arrest of growth from the age of approximately 9 to 10 years is appreciated, the height remaining at a level appropriate to this age. It is possible that it is in this group of cases alone that the absence of the normal pre-puberal and puberal growth spurt is contributory to the growth-failure. This view is supported by the appreciable increment of 1¼ in. in height recorded after three months of treatment confined to œstrogens.

Turner (1938) linked the failure of sexual development and of skeletal growth in these cases within the term "sexual infantilism". Growth-failure is, however, by no means invariably associated with this particular gonad defect, and does not, for example, occur in girls who have suffered pre-puberal castration. Available evidence suggests that the growth-failure is an associated defect, either genetically determined or induced as a result of a mutually injurious influence operating in the 5–17 mm. phase of embryogenesis. The cortex of the primitive genital ridge at this stage appears to be undergoing organization for the process of penetration by the primordial germ cells—their sex already genetically pre-determined—which migrate from the endoderm of the yolk sac. Upon this penetration further sexual differentiation of the gonad would seem to depend (Witschi, 1951). With failure of this process cortical elements specific to the sex of the gonad would not emerge, whereas medullary rudiments would be relatively unaffected thus persisting as in this and other like cases.

Title of syndrome.—Although Turner in 1938 emphasized the element of sexual infantilism associated with the stigmata referred to, this particular elaboration of the webbing syndrome had been noted previously, principally in the course of codification of its various forms by Ullrich in 1930, with whose name the syndrome is still firmly associated in Continental schools. Hence the suggested compromise title of the syndrome.

REFERENCES

Atkinson, W. B., and Eleftman, H. (1945) *Anat. Rec.*, **91**, 7.

Turner, H. H. (1938) *Endocrinology*, **23**, 566.

Ullrich, O. (1930) *Z. Kinderheilk.*, **49**, 271.

Witschi, E. (1951) *Recent Progr. Hormone Res.*, **6**, 5.

Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*May* 27, 1952]

DISCUSSION: CLINICAL ASPECTS OF OCCUPATIONAL DISEASES

Dr. Donald Hunter (Physician in Charge, Department for Research in Industrial Medicine (Medical Research Council) The London Hospital):

The Teaching of Occupational Medicine

The study of occupational health is as much a specialty as any other branch of medicine. The full-time industrial doctor of the future must be so well trained that he will be invited to co-operate with managers, workers, engineers, chemists and architects. He should aim at discovering all possible faults in the working environment with a view to finding proper remedies for them. He must, therefore, learn a great deal which is non-medical before his job becomes intelligible. His knowledge of the complex environment of the worker in a dangerous trade can be learned only by his continued presence at the place of work, and he must be recognized by his colleagues and by industry as being proficient in this field (Swanston, 1952). But the average medical student will not become a full-time doctor employed in a factory—what then should he or she be taught? I will outline how we teach the subject at the London Hospital. Before the student ever gets to the wards he has attended two lectures upon occupational diseases as part of a course of instruction on the social background of the patient. In the first of these a man with lead poisoning is questioned and examined by one student of the class beforehand. He is coached by a registrar as to leading questions and usually produces a good occupational history. In the second lecture, the same thing happens in the case of a patient with silicosis.

The lecturer begins by pointing out that a man's occupation is important apart from the dangerous trades. One would not allow a man convalescent from pulmonary tuberculosis who belongs to the tailoring trade to go on working ten hours a day as a presser wielding a 16-lb. iron. A brief description is given of inconsistencies in the names of certain trades and occupations. The student is warned that a man cleaning a casting with a compressed air chisel is known as a steel dresser in the north of England but when he does the same job in the south he is called a fettler. He is told how men drilling and blasting rock in coal-mines are known as hard headers in South Wales, rippers in Durham and brushers in Kent. It is pointed out the name used for an occupation may mislead the doctor who is taking the history. Thus a bricklayer is not necessarily employed in building houses for he may demolish with a compressed air chisel furnace linings made of special refractory bricks containing 80 per cent of silica. A man who calls himself an engineer's fitter may do his work on chromium plating vats and thus encounter the hazard of chrome dermatitis. In a similar way a glassblower may be exposed to the hazard of mercury poisoning if he does his work in a thermometer factory.

Lantern slides are then shown to indicate good and bad conditions in the manufacture of white lead and electric accumulators. The axioms of Sir Thomas Legge are shown on lantern slides.

I shall lay stress on some axioms which experience has led me to enunciate: (1) Unless and until the employer has done everything—and everything means a good deal—the workman can do next to nothing to protect himself, although he is naturally willing enough to do his share.

(2) If you can bring an influence to bear external to the workman (i.e. one over which he can exercise no control) you will be successful; and if you cannot or do not, you will never be wholly successful.

(3) Practically all industrial lead poisoning is due to the inhalation of dust and fume; and if you stop their inhalation you will stop the poisoning.

(4) All workmen should be told something of the danger of the material with which they come into contact and not be left to find it out for themselves—sometimes at the cost of their lives.

(5) Examples of influences—useful up to a point, but not completely effective—which are not external, but depend on the will or whim of the worker to use them, are respirators, gloves, goggles, washing conveniences, and waterproof sand-paper (Legge, 1934).

In the second lecture lantern slides are shown to illustrate the methods of dust suppression in siliceous rock mining. The solubility theory of silicosis is then stated. The statutory duty of the doctor to notify cases of industrial disease and poisoning is pointed out, and the work of the Factory Department of the Ministry of Labour is described briefly.

The patient is then brought into the lecture room and questioned by the lecturer. The student reads out the occupational history and is interrupted at suitable points. He is instructed to take the occupational history from the time of leaving school and to itemize the periods and nature of employments in chronological order. He is told that each separate employment should be amplified by reference to the materials, the tools, the processes, the general environmental conditions and the protective devices in use. The need to ask whether any similar illness has occurred in fellow workmen is mentioned (Meiklejohn, 1949). The lecturer goes on to demonstrate such physical signs as wrist-drop, indicating how the various muscle groups are tested clinically. In the second lecture he indicates how the chest is examined and explains the X-rays. The patient is then thanked for having given up his time and dismissed. The remainder of the lecture session is taken up by a general discussion. The lecturer makes it clear that there are few surer and quicker means of gaining a patient's confidence than the display of intelligent knowledge of his job. The workman has his own notions, and he may be governed very much in his thinking by the mass opinions of his fellow-workers. The London artisan is usually intelligent and co-operative and often a good witness, but what if he be deaf, disconsolate, forgetful or obtuse? He may be either garrulous or monosyllabic, but in spite of all these possibilities he is still the best witness to what has happened and should be handled with great patience and understanding (O'Donovan, 1952).

During the whole period of clinical instruction this technique of history taking is inculcated and developed. Physicians teaching in the wards and in the out-patients department are urged to emphasize the importance of the occupational background. During his periods of ward clerking the student attends ten lectures devoted to occupational diseases in the course on preventive medicine. By means of lantern slides he is shown in detail the worst and the best conditions in every sort of occupation, industrial, agricultural and other. He is taught to realize that he cannot do his best for his patients unless he studies the conditions under which they work in factory, mine, quarry, dock, shipyard, office, shop or the various transport services. No doctor can be expected to be familiar with the details of all occupations but he should take every opportunity to study the industries within the area of his practice. The student is told that only a fraction of a nation's work is done by large firms and the smaller firms must always look for help to the general practitioner: there is nothing in the nature of industrial medicine which is beyond the competence of a sound practitioner. The photographs chosen for lantern slides must, of course, show perfect definition and must illustrate important general principles. The student is told that it is not necessary for him to learn complicated chemical formulæ, but, whether he works in a factory or not, he must as a practising doctor know something of the chemistry of industrial processes, and of the toxicological risks in dangerous trades. For example, the metallic poisons have entirely different effects depending on whether they exist in organic or inorganic form, whether their physical properties are those of a solid, a liquid or a gas, whether the valency of the metal radicle is high or low, and whether they fall upon the skin or enter the body through the respiratory or alimentary tracts. Industrial arsenic poisoning occurs in two forms, the first from inhalation of, or contact with, the dusts of compounds of arsenic, and the second from inhalation of arseniuretted hydrogen. The symptoms in the two groups bear little or no resemblance to one another. The compounds of arsenic act as local irritants to the skin and mucous membranes, giving rise to dermatitis, papilloma and even carcinoma of the skin, conjunctivitis, coryza, laryngitis and even perforation of the nasal septum. Polyneuritis does not arise, and only rarely is the dose of arsenic large enough to produce the gastro-enteritis so common in the criminal administration of arsenic. Arseniuretted hydrogen, on the other hand, acts as a powerful hæmolytic agent, causing hæmoglobinuria, anæmia and hæmolytic jaundice.

Apart from toxicology, the student is, of course, taught about special infections such as anthrax, glanders and Weil's disease. The effects of physical agents such as X-rays, radium and nuclear energy are not overlooked; neither are decompression sickness, heat cramps and the physical effects of vibrating tools. Needless to say, the dust diseases of the lungs are discussed in detail. Undergraduate students are taken on two conducted visits to factories, usually a white lead works and an asbestos factory.

The postgraduate student who intends to become a full-time industrial medical officer must, of course, receive lengthy instruction in medical statistics, ventilation, lighting, heating, sanitation, working conditions, hours of work, welfare, safety, noise, weight lifting, posture problems, seating, boredom, canteens, sick absence, medical and nursing services, rehabilitation and resettlement (Stewart, 1944). He must know something of what is laid down in the Factories Acts, and in the

National Insurance (Industrial Injuries) Act. In addition to visits to factories for purposes of instruction he is required to live in certain factories for many weeks at a time. Only by so doing can he begin to appreciate the complex problems which have to be solved by the industrial medical officer of to-day.

REFERENCES

LEGGE, T. (1934) Industrial Maladies. London.
MELLEJOHN, A. (1949) *Lancet* (ii), 360.
O'DONOVAN, W. J. (1952) *Trans. Ass. indust. med. Off.*, **2**, 34.
STEWART, D. (1944) *Proc. R. Soc. Med.*, **37**, 244.
SWANSTON, C. (1952) *Brit. med. J.* (i), 1131.

Dr. R. S. F. Schilling (Reader, Nuffield Department of Occupational Health, University of Manchester):

Byssinosis in the British Cotton Industry

Byssinosis is a respiratory disease occurring among cotton workers exposed to fine dust. Greenhow, who was a lecturer in Public Health at St. Thomas's Hospital, gave one of the earliest descriptions of it in 1860. In spite of its long standing neither the fraction of cotton dust which causes it nor its exact mode of action is known. It is principally a disease of Lancashire where the British cotton-spinning industry is concentrated in towns like Oldham, Rochdale, Bury and Bolton.

Raw cotton arrives in this country in tightly compressed bales which are opened in the cotton chamber or opening room. The cotton is then cleaned by removing short fibres, dust and dirt by a pressure-blowing process in the blowing room. The cotton, now partially cleaned, passes in the form of a lap to the card room where the cotton fibres are further cleaned and drawn out into parallel lines by the carding engine.

The disease occurs among men who have worked for several years in the opening room, blow room or card room but spinners and weavers are not affected. It is the card room workers who suffer most from the disease, particularly the strippers and grinders who clean and grind the teeth of the carding engines which get clogged up with fine dirt and cotton dust. In the past the stripping of carding engines was a very dusty job and can still be so if proper precautions are not taken.

Byssinosis has three stages. The first stage develops after the worker has been exposed to dust for some years, usually about ten. Some men may have their first symptoms sooner than this and some much later. Others are never affected by the dust in any way. The worker complains of tightness of his chest and shortness of breath when he returns to work after a short absence—characteristically after the week-end break. Hence it has been called the "Monday feeling or fever". It usually lasts until he gets home in the evening. By Tuesday he has completely recovered and will remain free from symptoms until the following Monday. This condition may persist without getting any worse until the worker leaves the industry.

In the second stage symptoms get progressively worse on Mondays and eventually the worker has the same symptoms on other days. If he leaves the industry he will recover completely and will have no obvious disability. But many men who reach the second stage of the disease do not leave the industry and pass into the third stage of disabling byssinosis. The symptoms of tightness of the chest and dyspnœa are so distressing that the worker has to leave the cotton industry. Yet he will have some relief when he is away from cotton dust, but the dyspnœa remains as a permanent disability. Post-mortem examinations have shown that these men have an advanced emphysema (Shaw Dunn and Sheehan, 1932); but there is no fibrosis, and in life there are no characteristic X-ray changes.

The exact mode of action of the cotton dust is not known. The natural history of the disease suggests that there is an allergen in cotton dust which sensitizes the bronchial mucous membrane and produces bronchospasm and possibly swelling of the mucous membrane. After prolonged exposure this leads to emphysema. But recent work by Caton, Furness and Maitland (1952) does not confirm this hypothesis. They prepared different extracts of cotton dust and did skin tests on men with mild and severe symptoms of byssinosis and on men who had worked in cotton card rooms without symptoms, and on others who had never worked in a cotton mill. Those who had a wheal and flare type of reaction were equally distributed between all these groups. This reaction probably indicates hypersensitivity to cotton dust but it does not indicate a hypersensitivity specific to byssinosis.

The morbidity and mortality rates of men working in the cotton industry emphasize how serious the effects of exposure to fine cotton dust can be.

Bradford Hill (1930) compared the sickness experience of strippers and grinders with that of warehousemen and ring-room spinners in the period 1923–27. He showed that after the age of 30 sickness due to respiratory disease was for the strippers and grinders three times as high as for those working in the same industry but not in the dusty rooms. Death-rates from respiratory diseases in the triennium 1930–32 were equally striking. For strippers and grinders over 55 the respiratory mortality was at least three times as great as for men working in other parts of the cotton mill. But the respiratory mortality of strippers and grinders declined appreciably between 1920 and 1930. This was no doubt to some extent due to the recession in the trade at this time and the consequent reduction in the time spent in the mills; but in the previous decade attempts had been made with some success to

enclose the stripping brush and to remove the dust by exhaust ventilation. This no doubt also had a beneficial effect on the death-rates. Since then there have been further improvements in methods of dust control in the card rooms, by air conditioning, by vacuum cleaning the carding engine which reduces considerably the number of times the engine has to be stripped. Oiling of the cotton before it is blown and carded is a more recent method of suppressing the dust and there is evidence from card-room dust-counts, before and after oiling, that it is successful (Chief Inspector of Factories, 1949).

Nevertheless, in spite of these improvements a substantial number of men employed in the dustier mills spinning the coarser grades of cotton were found by Schilling, Goodman and O'Sullivan (1952) to be suffering from the disease. Of 131 men over the age of 35 with at least ten years' exposure in card and blow rooms, 45 had no symptoms, 52 were in the first stage of the disease and 16 and 15 in the second and third stages respectively. 3 men could not be graded because of incomplete histories.

There could be a more effective control of the disease if medical supervision and engineering control of dust were combined. There is at present no system of periodical medical examination of card-room workers. If there were, the incidence and severity of the disease found would indicate the mills where improved methods of dust control were needed, and the men who were getting progressively worse and who should be encouraged to leave the industry or work in the less dusty mills.

Since the end of the last century the Registrar-Generals of England and Wales have noted that cotton workers have a high death-rate from the cardiovascular-renal group of diseases. In his evidence to the Departmental Committee on Dust in Card Rooms (1932) Dr. Stevenson, representing the Registrar-General, suggested that the circulatory type of disease was a more important occupational

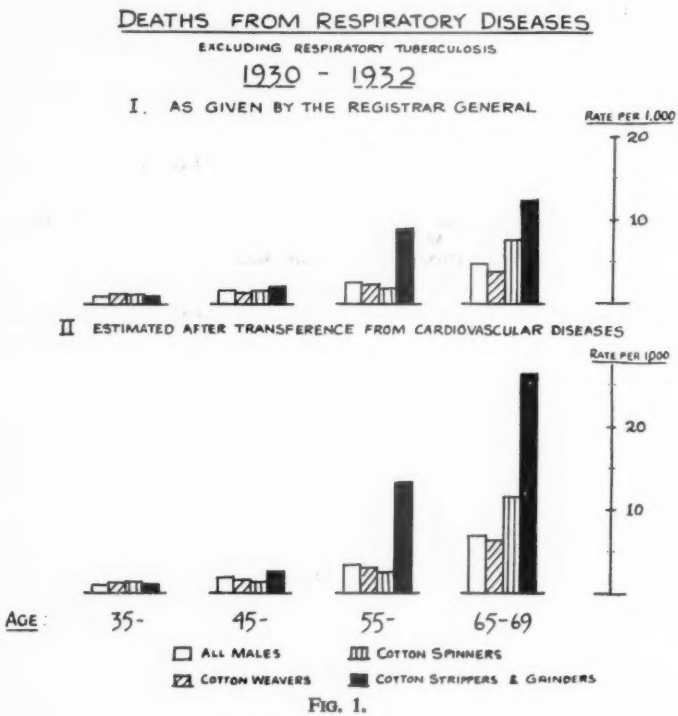

FIG. 1.

risk for card-room workers than respiratory disease. But there is a simple reason for at least a proportion of this cardiovascular mortality excess recorded by the Registrar-General. General practitioners, more often than not, put down at least two causes of death on the death certificate. The Registrar-General has to choose one for his statistical calculations. Before 1939 any cardiovascular-renal disease took preference over a respiratory disease. These rules for selection have since been changed and preference is now given to the disease which started the pathological changes leading to death. The effects of these changes have been estimated statistically (Schilling and Goodman, 1951) and the extent to which the respiratory death-rates of cotton workers had been underestimated is shown in Fig. 1. Nevertheless after these corrections have been made there still appears to be an

TABLE I.—MEAN SYSTOLIC AND DIASTOLIC PRESSURES AND INCIDENCE OF HYPERTENSION IN CARD- AND BLOW-ROOM WORKERS AND WEAVERS AND WAREHOUSEMEN

	Card- and blow-room workers	Weavers and warehousemen
Number of men (aged 50–59)	59	50
Mean systolic pressures	137·9*	129·9*
S.E. of mean	2·8	2·2
Mean diastolic pressures	84·9	81·6
S.E. of mean	1·4	1·3
Lowest pressures at or above 150/90	15*	4*

*P<0·05.

excess of cardiovascular deaths among strippers and grinders. In the recent clinical investigation of cotton workers by Schilling, Goodman and O'Sullivan, there was a significantly higher incidence of hypertension among the card- and blow-room workers aged 50–59 than among weavers and warehousemen of the same age, as shown in Table I. This could not be explained by observer error, heredity or anthropometric differences between the groups. In this group there was a suggestive correlation between the height of the systemic blood pressure and the stage of the industrial respiratory disease. A similar observation was made by Heimann and his colleagues (1950) in Illinois foundrymen among whom elevated systemic blood pressure levels were related to increasing degrees of pulmonary fibrosis.

This finding among cotton workers will be investigated in more detail but it may be that it is now too late to find anything of real significance because of the improvements in methods of dust control. Moreover this type of field investigation has to be made in the factories where management will co-operate and these are usually the workplaces with the best conditions.

REFERENCES

CATON, R. H., FURNESS, G., and MAITLAND, H. B. (1952) *Brit. J. industr. Med.* (In the press.)

Chief Inspector of Factories (1949) Annual Report for the Year 1948. (Cmd. 7839) H.M.S.O. London.

GREENHOW, E. H. (1860) Report of the Medical Officer to the Privy Council. Third Report. London.

HEIMANN, H. *et al.* (1950) in Health of Ferrous Foundrymen in Illinois (U.S.P.H.S. and Illinois Dept. of Public Health) Washington.

HILL, A. B. (1930) *Report of the Industrial Health Research Board*, No. 59. H.M.S.O. London.

SCHILLING, R. S. F., and GOODMAN, N. M. (1951) *Brit. J. industr. Med.*, **8**, 77.

——, ——, and O'SULLIVAN, J. G. (1952) *Brit. J. industr. Med.*, **9**, 146.

SHAW DUNN, J., and SHEEHAN, H. L. (1932) Report of Departmental Committee on Dust in Card Rooms. Home Office. H.M.S.O. London.

STEVENSON, T. H. C. (1932) Report of Departmental Committee on Dust in Card Rooms. Home Office. H.M.S.O. London.

Dr. A. I. G. McLaughlin (H.M. Medical Inspector of Factories).

The Diagnosis of the Occupational Dust Diseases of the Lungs

The diagnosis of the dust diseases depends on evidence derived from the occupational history, the clinical examination and the X-ray examination. The final court of appeal is, of course, the autopsy with histological, chemical and petrological examination of the lungs. The pneumoconioses cannot be diagnosed without an X-ray film of the chest, but it is not possible to come to a diagnosis on the X-ray film alone. The X-ray appearances of all dusty lungs, except cases of asbestosis, have a basic pattern, because the dust aggregates are found mainly in the peribronchial and periarterial lymph channels and nodes.

For the purpose of this discussion, I propose to take the X-ray picture of uncomplicated silicosis, in which there are nodular or miliary shadows distributed more or less evenly over both lung fields and to show that many other conditions could be mistaken for it.

Table I is a list of the industrial pulmonary diseases in which the X-ray picture resembles that of silicosis in the stage of nodulation.

TABLE I.—INDUSTRIAL PULMONARY LESIONS WITH X-RAY PICTURES LIKE SILICOSIS

Organic Dusts	*Inorganic Dusts*	
Bagassosis (bagasse or sugar cane)	Coal-miner's pneumoconiosis	
Tabacosis (tobacco dust)	Beryllium granulomatosis	
Farmer's lung (mouldy hay)	Talc pneumoconiosis	
Leather worker's lung (? leather dust)	Asbestosis	
Byssinosis (cotton dust) rarely	Siderosis (iron)	Opaque dusts
	Baritosis (barium)	
	Stannosis (tin)	
	Emery	

Table II gives a list of the non-industrial pulmonary lesions which might be mistaken for silicosis.

TABLE II.—NON-INDUSTRIAL PULMONARY LESIONS WITH X-RAY PICTURES LIKE SILICOSIS

Miliary tuberculosis		Œdema of lungs (some cases)
Sarcoidosis		Bronchiolitis and bronchiolectasis
Pulmonary hæmosiderosis	Mycoses	Aspergillosis (occasionally industrial)
Carcinomatosis		Moniliasis
Vascular lung changes, e.g. erythræmia		Coccidio-mycosis
Miliary calcified nodules		Blastomycosis
Wheatena (? histoplasmosis)		Actinomycosis (sometimes occupational)

It will be seen that the conditions which simulate the X-ray picture of silicosis make a long list and no doubt other lesions can be added to it. For instance, the cases of "honeycomb lungs" described by Oswald and Parkinson (1949) and Parkinson (1949), and some cases of mite-infection of the lungs might be added to it.

It is clear that, when so many conditions have comparable X-ray changes, a diagnosis must be made from additional evidence obtained from other methods of examination. In the industrial cases the occupational history is of paramount importance, but a clinical examination is also necessary. By clinical examination I mean all the procedures designed to establish whether disease or disability is present. The help of the clinical pathologist and the physiologist is essential.

ILLUSTRATIVE CASES

I have examples of some of the conditions listed in Tables I and II and brief notes about them are given.

(1) *Silicosis.*—Fig. 1 shows the X-ray appearances of silicosis in the stage of nodulation. He was a man of 49 years of age and he had been a steel dresser or fettler since leaving school at 14 years of age. An uncomplicated occupational history like this is not often obtained. He was still working when I examined him, but he complained of cough, expectoration and moderate dyspnœa. These symptoms had been noticed for about five years and they were gradually becoming more marked. Owing to the fact that he was lame I could not estimate his tolerance to exercise. The chest excursion was 1½ in. and the percussion note was impaired over the upper halves of both lung fields with post-tussic crepitations heard over the same areas. He was apyrexial and no tubercle bacilli were found in the sputum. There was little doubt that this man had silicosis because he had been exposed for a number of years to dust containing free silica. The diagnosis, therefore, was made mainly on the occupational history.

Fig. 9 (McLaughlin *et al.*, 1950) shows the histological lesions which cast the shadows seen in the X-ray film. They consist of a number of classical silicotic nodules.

(2) *Leather worker's lung.*—Fig. 2 shows the X-ray appearances of a leather worker's lung. He was a man of 46 years who had been a leather dresser since leaving school at 14 years of age, i.e. for thirty-two years. He had been exposed to the inhalation of a mixed dust containing leather with smaller quantities of china clay, carborundum and calcium carbonate. He had no cough or sputum but he complained of slight dyspnœa on exertion. Clinical examination revealed little abnormality except that the percussion note was slightly impaired over both upper zones and that the breath sounds were diminished over the whole of the lung fields. His exercise tolerance test and cardiac response to effort were normal. From the occupational history this man cannot be diagnosed as silicosis because he had not been exposed to the dust of free silica. The X-ray appearances, however, resemble those of silicosis. It is not yet known what are the histological changes in the lungs which cause these X-ray shadows.

(3) *Talc pneumoconiosis.*—Fig. 3 shows the X-ray appearances in a case of talc pneumoconiosis. This case has been previously published (McLaughlin, Rogers and Dunham, 1949). The man was 51 years of age and had worked in a rubber-tyre factory since he left school at 14 years. The only industrial dust to which he was exposed was that of talc. The X-ray film shows nodular shadows distributed over both lung fields. For two years he complained of increasing dyspnœa, which was partly due to aortic regurgitation. At autopsy he was found to have widespread nodular fibrosis (Fig. 10). In addition there were "curious bodies" rather like the asbestosis body and in some respects the histological picture resembled asbestosis. Talc consists of plates with a small percentage of fibres, but only the latter were found in the lungs. In this case, too, the X-ray appearances could have been interpreted (wrongly) as silicosis.

(4) *Coal-miner's pneumoconiosis.*—The X-ray appearances of a man of 37 years of age who had been a coal-miner for twenty years and a sand-blaster in an iron foundry for two and a half years are shown in Fig. 4. These abnormalities were found on routine medical examination. They are similar to those shown in Figs. 1, 2 and 3. The man's main industrial exposure had been to coal-dust in South Wales (Rhondda Valley) but probably his work as a sand-blaster in an iron foundry has also contributed to the picture. He complained only of occasional shortness of breath on exertion and on clinical examination no abnormal signs were found. Even with the occupational history it is not possible to say whether the X-ray abnormalities are the result of coal-miner's pneumoconiosis or silicosis or a combination of the two conditions.

(5) *Beryllium granulomatosis.*—Another lesion which has a similar X-ray picture is beryllium granulomatosis. Such cases are rare in this country, but those which have occurred show X-ray appearances comparable with those of silicosis. In addition there is marked loss of weight and dyspnœa, and one case at least was diagnosed as miliary tuberculosis before the occupational history of exposure to dust containing beryllium gave the clue to the diagnosis. The picture could easily be regarded as consistent with a diagnosis of silicosis and in the fluorescent lamp industry, where the dust to which the workers have been exposed contains silica, as well as beryllium oxide, such a diagnosis would not be unreasonable.

(6) *Miliary tuberculosis.*—Fig. 5 is an X-ray film of the chest of a case of acute miliary tuberculosis. The appearances are not unlike those of the pneumoconioses, but the clinical features of pyrexia, tachycardia, and cyanosis, together with the other features of tuberculosis, usually leave little doubt about the diagnosis.

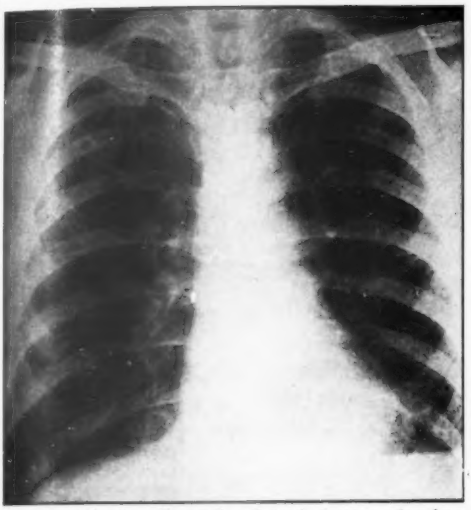

FIG. 1.—Chest radiograph of steel dresser, showing generalized nodular shadows—uncomplicated silicosis.

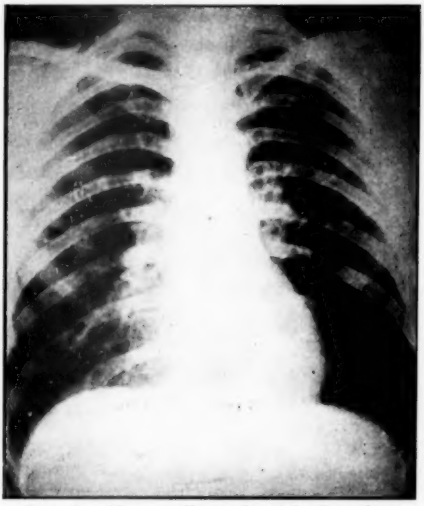

FIG. 2.—Chest radiograph of leather dresser showing generalized nodulation—a pneumoconiosis but not silicosis.

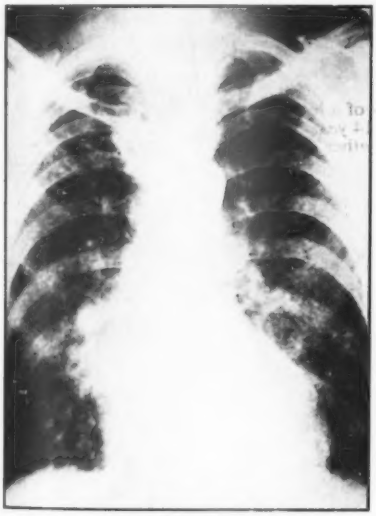

FIG. 3.—Chest radiograph of rubber worker exposed to talc dust, showing generalized nodular shadows and large heart shadow—talc pneumoconiosis.

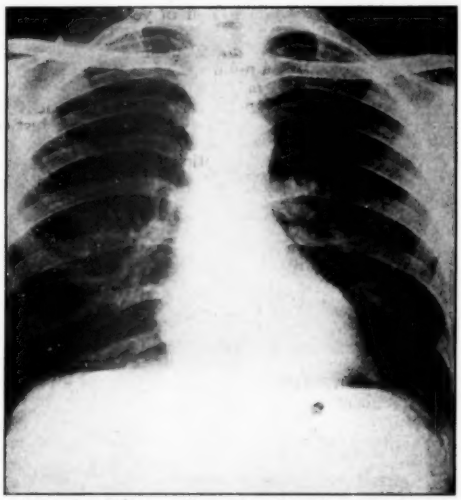

FIG. 4.—Chest radiograph of coal-miner (twenty years) and sand-blaster (two and a half years), showing generalized nodular shadows—coal-miners' pneumoconiosis and/or silicosis.

(7) *Sarcoidosis.*—The X-ray picture of sarcoidosis resembles that of miliary tuberculosis and the pneumoconioses. It will be recalled that the early cases of beryllium granulomatosis in the United States were first labelled as Boeck's sarcoidosis.

It is my contention that, if one only had the X-ray film to go on, it would not be possible to differentiate either miliary tuberculosis or sarcoidosis from the pneumoconioses.

(8) *Opaque dusts.*—The difficulty of making a diagnosis on the X-ray film alone is illustrated by considering the dusts which are opaque to X-rays. In recent years there have been studies of various groups of workers who have been inhaling metallic dusts such as iron or its oxides, tin, emery and barium. The X-ray appearances in these cases are surprisingly like those of uncomplicated silicosis and hence of miliary tuberculosis and sarcoidosis and yet there is little or no evidence of disability or illness of any kind.

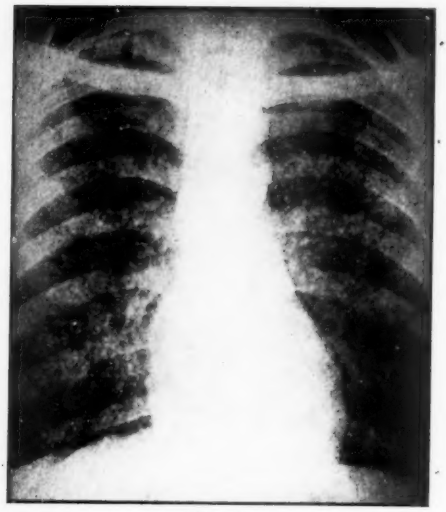

FIG. 5.

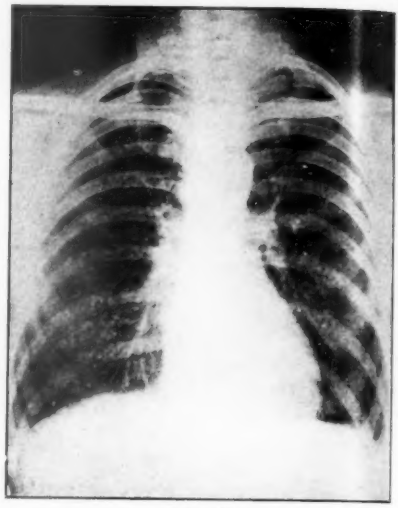

FIG. 6.

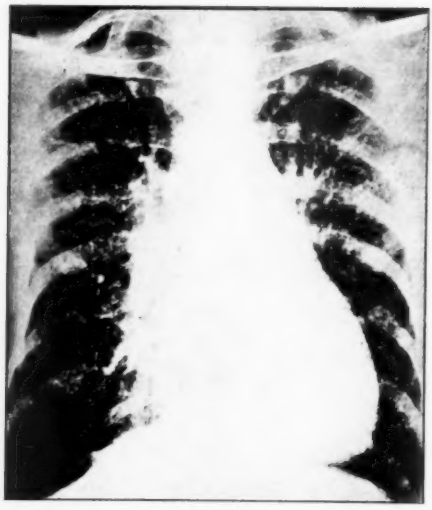

FIG. 7.

FIG. 5.—Chest radiograph of case of miliary tuberculosis—compare with Figs. 1, 2, 3 and 4.

FIG. 6.—Chest radiograph of an electric arc welder, showing generalized nodulation caused by deposits of iron oxide in the lungs—welders' siderosis.

FIG. 7.—Chest radiograph of a case of hæmosiderosis—generalized nodulation and "mitralized" heart shadow.

In the case of *iron* and its oxides it has been shown conclusively that it does not cause pulmonary fibrosis, though siderosis, when it was first described by Zenker in 1866 as a fibrosis of the lungs due to the inhalation of iron dust, is the oldest of the pneumoconioses. His original 2 cases both had pulmonary tuberculosis and such fibrosis as he found in the lungs may well have resulted from infection with the tubercle bacillus. Up to 1930 only 30 cases of siderosis (as a fibrosis of lung) had been described, and many of them had been inhaling free silica as well as iron dust. Recent interest in the effects of iron on the lungs was roused by the publication in 1934 of Stewart and Fauld's paper on the hæmatite miners. Hæmatite is an iron oxide (Fe_2O_3) and it occurs in association with quartz or free silica. When inhaled over a period of years it causes a fibrosis of the lung, which is really a sidero-silicosis, often associated with tuberculosis. Occasionally, as Craw has shown, there are cases with well-marked X-ray changes of the nodular and miliary type, but without fibrosis or tuberculosis of the lungs.

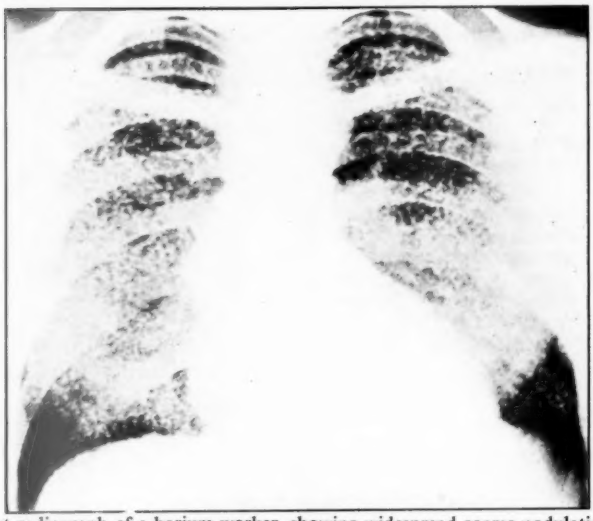

FIG. 8.—Chest radiograph of a barium worker, showing widespread coarse nodulation—baritosis.

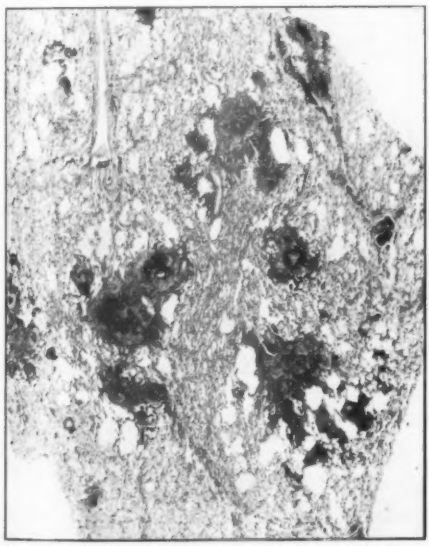

FIG. 9.—Section of lung of steel dresser showing silicotic nodules and focal emphysema. (× 5.)

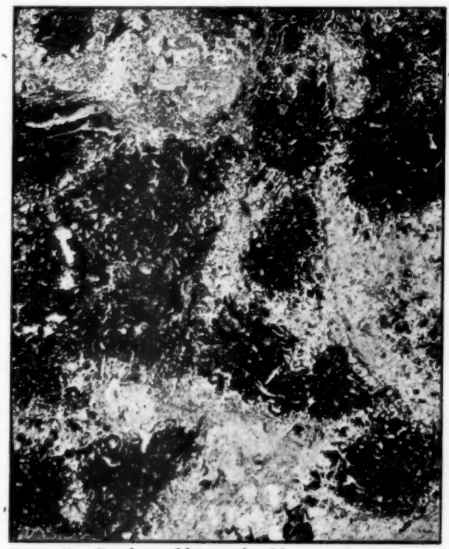

FIG. 10.—Section of lung of rubber worker exposed to talc dust, showing fibrotic nodules. (× 8.)

Electric arc welders inhale the blue-grey fume which arises from the welding operation, and this fume is composed very largely of iron oxide. Doig and I drew attention in 1936 to the abnormal X-ray appearances which are found in welders who have been engaged for over ten years at the job, but who show no clinical evidence of disability. An example of the typical X-ray picture of welder's siderosis is given in Fig. 6. We have found these appearances in a large number of welders and in none of them has there been disability. Such cases are from time to time diagnosed as miliary tuberculosis and I have had to rescue several of them from sanatoria. We have been on the look-out for autopsies on welders for about fifteen years and so far have not found one. This in itself is fairly good evidence that welding fume does not do a great deal of damage to the lungs.

The only published account of an autopsy on a welder who had shown the characteristic X-ray picture during life comes from the U.S.A. (Enzer and Sander, 1938). The patient had been killed in an accident and on histological examination deposits of iron oxide were found in the lymph spaces round the vessels and bronchi, but there was no fibrosis in relation to the iron pigment.

Doig and I have one case in our series of welders in which clearing of the abnormal shadows took place. He had developed the typical X-ray picture after eleven years' exposure to the fume of welding. During another eleven years, when he was no longer exposed, the shadows gradually became less in intensity and finally disappeared. By contrast, in cases of silicosis, the shadows tend either to extend or become more intense even if there is no more exposure to silica dust.

In silver finishers or polishers we have been able to get histological evidence of the effect of iron on the lungs. Articles of silver are polished with powders called rouge or crocus, both of which consist of pure or nearly pure iron oxide. The polishers inhale a good deal of dust during their working lives. After about twenty years' exposure they develop generalized reticular or nodular shadows in their chest X-ray films, but these changes are not associated with symptoms of illness or disability. One of our cases died after an operation for gastric ulcer, and the histological appearances of his lungs are shown in Fig. 11. This is an unstained section of the lung showing aggregations of iron near a vessel. There is no fibrosis.

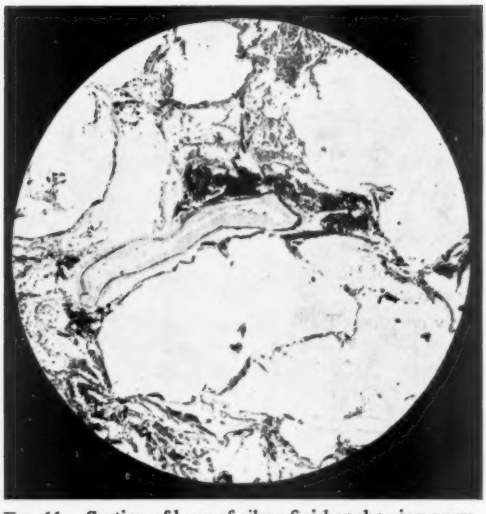

FIG. 11.—Section of lung of silver finisher showing aggregate of iron dust near a vessel: no fibrosis. (× 18.)

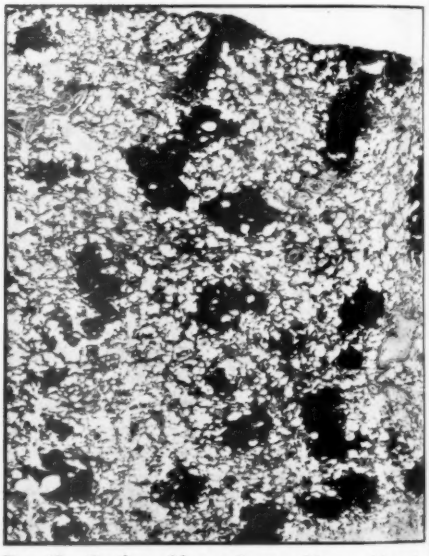

FIG. 12.—Section of lung of case of hæmosiderosis, showing aggregates of iron pigment in alveoli. (× 8.)

Iron can get into the lungs both through the inspired air and from the blood. In the focal forms of pulmonary hæmosiderosis, the X-ray pattern is like that seen in people who have been inhaling iron dust. It is likely that in both hæmosiderosis and industrial siderosis the abnormal shadows are due to the same cause, namely, that the aggregates of iron in the lungs are opaque to X-rays. Fig. 7 is the X-ray film of a case of hæmosiderosis secondary to mitral stenosis. The typical histological appearances of the lungs in this condition are shown in Fig. 12. The aggregates of iron are clearly shown, but in contrast with the histological picture of industrial siderosis, they occur more in groups of alveoli than in the peribronchial and periarterial lymph channels and nodes.

Another opaque dust is *emery*, which is composed of iron oxide (Fe_3O_4) and corundum, which is an aluminium oxide (Al_2O_3). Workers who are exposed for many years to the inhalation of the dust of emery show X-ray pictures similar to those described above, but again there are usually, in the absence of infective processes, no signs or symptoms of illness or disability.

Perhaps the most striking X-ray changes caused by an opaque dust are seen in the chest films of workers who have been inhaling the dust of barium. I might add that the density of the shadows thrown by these opaque dusts varies directly with the atomic weight of the metal—the higher the

atomic weight, the denser is the shadow. The atomic weight of iron is 56, while that of barium is 138. Fig. 8 is an X-ray chest film of an Italian worker engaged on the grinding of barytes. Most of these workers after some years' exposure show these alarming X-ray pictures, but I am told that they have no disability and that they do not get fibrosis of the lungs.

Conclusion

I think that the lessons to be learned from the foregoing observations are these:

(1) X-ray nodulation seen in chest films does not necessarily mean that fibrosis of the lungs is present. Aggregations of an inert opaque dust in the lungs can produce an X-ray picture like that seen in the uncomplicated pneumoconioses or in other pathological conditions.

(2) A diagnosis cannot be made from the X-ray film alone. It is necessary to have a full occupational history with details of exposure to the various dusts. And it is important to carry out a clinical examination as well.

Acknowledgments.—I am indebted to the Editors of the *Lancet* and the *British Journal of Industrial Medicine* for permission to reproduce Figs. 11 and 3 respectively; to Dr. H. E. Harding and Mr. A. W. Collins of Sheffield University for Figs. 9 and 10; to Professor Pancheri of Rome for Fig. 8; to Professor A. C. Lendrum of St. Andrew's University for Fig. 12; to Dr. Hugh Ramsay, Director of the Mass Radiography Unit, Wanstead Hospital, for Fig. 2, and to Mr. Collyer's Photographic Department of the Air Ministry for the prints of the radiographs.

REFERENCES

Doig, A. T. and McLaughlin, A. I. G. (1936) *Lancet* (i), 771.
Enzer, N., and Sander, O. A. (1938) *J. industr. Hyg. Toxicol.*, **20**, 333.
McLaughlin, A. I. G., Cheeseman, E. A., Garrad, J., Gloyne, S. R., Goodall, K. L., Harding, H. E., Jupe, M. H., Lawrie, W. B., Perry, K. M. A., Sutherland, C. L., and Woods, H. (1950) Industrial Lung Diseases of Iron and Steel Foundry Workers. London.
——, Rogers, E., and Dunham, K. C. (1949) *Brit. J. industr. Med.*, **6**, 184.
Oswald, N., and Parkinson, T. (1949) *Quart. J. Med.*, **18**, 1.
Parkinson, T. (1949) *Brit. med. J.* (i), 1029.
Stewart, M. J., and Faulds, J. S. (1934) *J. Path. Bact.*, **39**, 233.

Dr. A. Thelwall Jones (Consultant Physician, United Liverpool Hospitals):

Noxious Gases and Fumes

I shall limit my remarks to the insidious and possibly chronic effects resulting from exposure to noxious gases and fumes. I shall attempt to relate one or two common diseases to occupation rather than produce a catalogue of toxicology. Acute illness which can directly be attributed to occupation is rare and, in my experience, so is chronic ill-health. I speak comparatively with the overall picture of disease, but only recently have the possible chronic effects of work entered the field of serious scientific consideration. To those of us who have the privilege of studying disease in industry, a twofold responsibility occurs. Firstly, to initiate work to detect occupational causes. Secondly, and this is of very great importance, to keep a proper perspective of the incidence.

At the moment my evidence is largely negative. The main portal of all occupational hazards is the lungs and it is interesting and instructive to consider the effects of occupation on the lungs themselves. Workers in industry are exposed to a number of noxious fumes and gases which may be roughly classified as follows:

Classification

Asphyxiants.—(*a*) Simple inert gases displacing oxygen from the respiratory tract, e.g. nitrogen, carbon dioxide, nitrous oxide. (*b*) Chemical—interfering with the vascular respiratory mechanism, carbon monoxide, hydrogen cyanide, aniline, &c.

Centrally acting poisons.—Producing anæsthetic effects after absorption through the lungs. Hydrocarbons such as benzene and petrol, chloro-compounds, e.g. trichlorethylene, carbon tetrachloride and methyl bromide and the alcohols.

Miscellaneous.—The barbiturates. Hydrogen sulphide and carbon bisulphide.

Irritants.—(*a*) Acting on upper respiratory tract—ammonia, hydrochloric acid and sulphur dioxide. (*b*) Acting on upper respiratory tract and lungs—sulphur dioxide, chlorine, osmium. (*c*) Acting principally on the lungs—phosgene, nitrous fumes and nickel carbonyl. Beryllium, manganese, vanadium.

In view of the importance of predisposing factors such as heredity, overcrowding, heat, humidity and subsequent sweating, it is difficult to assess the effect of occupation on the incidence of bronchitis and pneumonia. It is generally assumed that exposure to high concentrations of industrial dusts

reduces resistance to acute respiratory infections, but it has been shown by Baetjer (1947) by animal experiments that variable results are obtained depending upon the type of dust. Most centrally acting poisons and asphyxiants, such as trichlorethylene and other volatile solvents, do not give rise to pneumonia except by aspiration. There is no evidence of an increased incidence of respiratory infections during the manufacture of trichlorethylene in workers exposed to small concentrations. Since the beginning of the Second World War, routine examinations of workers in industry have become common and these have certainly proved of value where specific ill-effects are being sought. This is in contradistinction to routine examinations of people in general with the forlorn hope of preventing the onset of disease and promoting ripe old age.

As an example, workers engaged in the manufacture of heavy chemicals have been examined over a period of ten years. Much labour is involved to decide if minor departures from normal are significant and if sickness can be in any way attributed to occupation.

After a short experience of routine examination in a particular process, it is probably better for the medical officer to inspect the plant at regular intervals and talk to the employees. If he secures their confidence, they will report ill-health at an early stage, which seems to be a much better procedure than the examination of "healthy men" by inadequate methods. The more experienced the physician, the more time he spends in listening to the history of the patient. It must not be thought, however, that ancillary methods such as blood and urine examinations are to be disregarded. I would also point out that certain chemicals are insidious poisons which can produce mental illness—possibly the anxiety states so prevalent to-day. Who knows what other factors in industry or diet can precipitate or aggravate the troubles of our time?

There is a host of irritating fumes and gases in industry, and I have picked chlorine as an example. Numbers of workers have been gassed and these also, with others, have been exposed to repeated small concentrations.

During the years 1932–48, 820 cases of chlorine gassing in workers on chemical processes have been observed by the writer and colleagues. Of these 728 were classified as mild and reported to the medical department with a painful cough and increased respiration. 81 had considerable respiratory embarrassment, with distended cervical veins and some cyanosis, and 11 were sent home after treatment. The pulse and respiratory rates were raised and the physical signs were those of bronchitis, medium rhonchi and rales being present on auscultation of the chest. 9 cases were severe and required admission to hospital, but even in these cases pulmonary œdema or pneumonia did not ensue. It is probable that in the First World War œdema and pneumonia ascribed to chlorine were due to mixtures of chlorine and phosgene. There is, however, other evidence, both clinical and experimental, reporting pneumonia.

A follow-up of severe cases (from the series of 820 already mentioned) which have occurred since 1936, does not reveal any clinical or radiological evidence of permanent damage to the respiratory tract. (7 X-rays shown.) Considerable numbers of workers are exposed to small daily doses of irritant gases. A clinical and radiological survey carried out during the past five years does not reveal any evidence of pulmonary damage. A study of death certificates and sickness absenteeism shows no excessive tendency towards the development of chronic bronchitis or emphysema.

It is my belief at present that there is little evidence of an occupational cause of chronic chest disease, although statistical proof of this is not yet advanced.

The development of pulmonary œdema following exposure to phosgene causes a desperate medical emergency and 6 cases have been successfully treated and personally observed since 1936. One case succumbed. In surviving patients recovery is apparently complete and there is no permanent damage to the lungs as shown by sickness records, clinical and radiological examination.

A normal chest X-ray is shown[1] of the most severe surviving case taken on November 14, 1949. The gassing occurred on January 9, 1936.

The action of the metallic fumes is of extraordinary interest and the following associations are now well known:

Mercury and erethism and tremors. *Manganese* and Parkinson's disease. *Beryllium* and pneumonitis. *Phosphorus* and necrosis of the jaw. *Fluorine* and chronic disease of the skeleton. *Vanadium* and bronchospasm. *Osmium* and bronchopneumonia.

Arsenic.—Quantities of arsenic are "about" in the heavy chemical industry, but I have yet to see a case of arsenical poisoning excepting those arising from arseniuretted hydrogen.

There appears to be an increased incidence of bronchial carcinoma in the nation, but this is not apparent in the chemical industry from a study of sickness and death records and from a radiological survey. A study of 100 cases failed to find any occupational or residential factor. Smoking has been suggested as a possible factor and the heavy smoking of cigarettes seems to be predisposing; it is of interest to note that cigarettes contain quite considerable quantities of arsenic.

Finally to remind us that diseases of the skin remain the most important occupational disability, I show two slides of acne.[1] These reveal the extraordinary result of exposure to the fumes of chlorinated naphthalenes, but this form of skin disease is rare in comparison with "dermatitis".

REFERENCE.—BAETJER, A. M. (1947), *J. industr. Hyg.*, **29**, 250.

[1]Not reproduced owing to lack of space.

Dr. N. D. Cruickshank (Medical Research Council Unit for Research on the Experimental Pathology of the Skin, Birmingham University):

Occupational Dermatitis and Industrial Skin Cancer

Occupational dermatitis.—In this contribution I shall describe briefly some investigations carried out in the Medical Research Council Industrial Medicine Research Unit under the direction of Professor J. R. Squire. The main results are published elsewhere (Squire *et al.*, 1950).

Analysis of the available National Statistics of industrial dermatitis based on the reports of the Examining Surgeons 1939–1946 showed a gradual increase in the numbers certified from 3,650 in 1939 to 9,190 in 1946. By using the figures available in the Annual Abstract of Statistics it was possible to compare the incidence in different industries by relating the numbers certified to the population at risk. This demonstrated that the rise in incidence during the war years had occurred in all industries and suggests that it was not due to bad conditions in any one industry but to some general social phenomenon. Whether the rise was due to an increase in the number of cases occurring or to a greater amount of certification cannot be stated.

Comparison of the incidences in different industries demonstrated that there were "high risk" industries, e.g. rubber and leather, with an incidence of 3·1/1,000/year as compared with the overall average of 1·5/1,000/year. These, however, contributed only a small proportion of the total cases. The largest number of cases arose in the engineering industry where the incidence was 1·0/1,000/year.

A special study of skin disease in a large engineering factory was carried out. At a weekly clinic held in the factory all cases of skin disease both in manual and in non-manual workers were seen.

Analysis by the site of occurrence of the skin disease of our patients showed that the manual workers carried an excess incidence of skin disease affecting the hand and forearm of some 4/1,000/year. The incidence of skin disease affecting other sites was the same in the two groups. This observation suggests that the manual workers are exposed to a special risk and it seems reasonable to attribute this to their working environment. Other differences between the two groups are considered less likely to be of importance.

Of the occupational groups within the factory, the majority of cases occurred in that large body of workers classified as machine operators. These men and their associated workers—tool setters and fitters, turners, &c.—are employed in the management and maintenance of the machine tool, and are usually exposed heavily to various cutting fluids or coolants. Though the largest number of cases are those within this group, certain occupations such as electroplating and soldering, painting and spraying, showed a higher incidence but numbers employed in these groups were not large.

Of the materials to which dermatitis could be attributed, the following seemed of importance: (1) Oil and cutting fluids. (2) Chrome and plating solutions. (3) Paraffin solvents and thinners. (4) Sensitizing drugs used in the treatment of minor injuries in the factory surgery.

It is to be noted that all of these are well-known hazards and have been so for years; clearly the application of existing knowledge would achieve considerable reduction in the dermatitis problem in industry.

When discussing industrial skin disease it is worth while bearing in mind the economic loss which occurs as a result of this condition. Investigation of the "compensation" cases occurring in 3 large Birmingham factories showed that on average a case of industrial skin disease loses ten weeks' work. On this basis half a million working days are lost annually.

Industrial skin cancer.—For information concerning the ætiology of industrial skin cancer we are greatly indebted to Dr. Henry's researches over the past twenty years (Henry, 1946, 1947, 1950). He has defined occupational groups with high and with low risks of skin cancer, and has demonstrated how exposure to carcinogens can be discovered in many occupations not obviously suspect.

From Henry's researches it would appear that the only large groups of industrial carcinogenic agents are firstly tar, pitch and associated substances and mineral oils (including shale oils). There are other possible skin cancer hazards in industry but at the moment at least they do not appear to be of significance.

The dangers associated with pitch and tar products are well recognized and several pure carcinogens have been isolated.

Less attention, however, has been paid to the carcinogenic properties of mineral oils—with the exception of those used in the cotton industry. Although carcinogenic oils have been used for many years in the cotton industry, so far no pure chemical carcinogen has been isolated from them. A possible reason why the dangers of mineral oils have received little attention is the fact that neither Factory Inspectorate records nor the researches of S. A. Henry demonstrated any excessive incidence of skin cancer in occupational groups outside the cotton industry. I propose to describe briefly reasons for regarding the oils used in engineering as potentially dangerous (Cruickshank and Squire, 1950; Cruickshank and Gourevitch, 1952).

Investigations of three kinds have been carried out in Birmingham:

(1) Field examination of workers heavily exposed to cutting oils.

(2) Biological tests on mice and rabbits.

(3) Surveys of patients treated for scrotal cancer or for cancer of the hand and forearm at the United Birmingham Hospitals.

Each of these has pointed to the carcinogenicity of mineral oils.

The first investigation was performed in three large Birmingham factories and involved the inspection of the hands and forearms of 138 machine operators. It was found that 80% suffered from oil folliculitis—indicating heavy exposure. The main interest, however, lay in the discovery of numerous hyperkeratotic lesions. These were of two types: raised, pigmented, rugose lesions, and flat, white warts. Both types of lesion have been described as occurring among mule spinners and are very similar to those found on the arms of tar workers. These warts were found on the arms of 33% of the workers. Analysis of the ages and exposure periods of the workers who had these lesions showed that the incidence significantly increased with the duration of exposure. Thus in the exposure group 0–5 years, the incidence was 13%; 6–10 years 35%; 11–15 years 38%; and 15 years and over 60%.

Since warty lesions such as these are frequently found where workers are exposed to carcinogens, they should be regarded as a serious indication of a cancer risk. Subsequent tests of a sample of one of the oils upon mice and rabbits showed that it produced papillomata not upon the mice but upon the rabbits.

If the oils used in the engineering industry were carcinogenic some evidence of this should be obtainable from a study of hospital records in the Birmingham area. This evidence was obtained by classifying by occupation all male patients who had been treated for hand and forearm, and for scrotal cancer at the United Birmingham Hospitals for the past ten years.

It was found that during this period there had been 34 scrotal and 44 hand and forearm cancers. Of these, 18 hand and forearm and 12 scrotal cancers had been exposed to oil; 6 hand and forearm and 13 scrotal cancers had been exposed to pitch, &c.; and 20 hand and forearm and 9 scrotal cancers had been exposed to other agents, i.e. between one-third and one-half of the patients gave a history of exposure to oil, and of these the majority had been employed in the engineering industry. Occupations frequently listed were machine operator, tool setter and tool smith—all of which categories are associated with the operating of machine tools.

The investigation was carried a stage further by comparing the incidence of skin cancer of these sites with the population at risk. A denominator was obtained by using the Registrar-General's Census Reports of 1931. In view of the long exposure and latent periods required for the initiating of skin cancer, the use of these figures is probably apt. Classification of the patients into the Registrar-General's 32 Orders and comparing numbers in each group with the population at risk showed that Group VII, which includes the majority of engineering workers, had a significantly increased incidence of skin cancer of these sites.

It is clear then that a prima facie case has been made out for regarding oils in use in the engineering industry as potentially carcinogenic. The question remains as to the best method of tackling the problem. Clearly, for many years to come we will be dependent upon splash guards, cleansing agents and the methods of preventive medicine. As a long-term policy, however, this is not entirely satisfactory. The ideal is to develop oils which are non-carcinogenic; or at least to define those oils which are least carcinogenic. At the moment the Medical Research Council Committee on the Carcinogenicity of Mineral Oils is dealing with this problem in association with the Institute of Petroleum.

Pioneer work was done in this field by Twort and Twort (1931, 1933), but the index which they prepared has been shown by Auld (1938) to be unreliable.

The investigations being undertaken at the moment, however, cannot be expected to yield immediate practical results. We are thus forced in the meantime to increase our vigilance over measures designed to minimize the contact of the worker's skin with oil.

REFERENCES

AULD, S. J. M. (1938) *J. Instn. Petrol. Tech.*, **24**, 577.

CRUICKSHANK, C. N. D., and GOUREVITCH, A. (1952) *Brit. J. industr. Med.*, **9**, 74.

——, and SQUIRE, J. R. (1950) *Brit. J. industr. Med.*, **7**, 1.

HENRY, S. A. (1946) Cancer of the Scrotum in Relation to Occupation. London.

—— (1947) *Brit. med. Bull.*, **4**, 389.

—— (1950) *Ann. roy. Coll. Surg. Engl.*, **7**, 425.

SQUIRE, J. R., CRUICKSHANK, C. N. D., and TOPLEY, E. (1950) *Brit. J. industr. Med.*, **7**, 28.

TWORT, C. C., and TWORT, J. M. (1931) *J. industr. Hyg.*, **13**, 204.

——, —— (1933) *Amer. J. Cancer*, **17**, 293.

Section of Psychiatry

President—DESMOND CURRAN, F.R.C.P., D.P.M.

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Enquiries Into Attempted Suicide [*Abridged*]

By E. STENGEL, M.D., M.R.C.P.

THERE must be many reasons, rational and irrational, why the problem of suicide is so rarely discussed by psychiatrists at their meetings, although in their practice it haunts them continually. It is worth remembering that we owe much of what is known about suicide to the work of non-medical men, expecially to sociologists. Durkheim's monograph in 1897, only recently translated into English (1951), has remained one of the most important books ever written on this subject. That author conceived suicide to be the outcome of social forces against which the individual was powerless. He did not hesitate to enter the fields of psychopathology and social therapy, and many of his observations, especially those relating to the effects of social disintegration on the suicide rate, have stood the test of time; some of the remedies he advocated, if phrased in modern language, would do credit to social psychiatrists. Durkheim's successors, though not equally emphatic about the exclusive importance of social forces, did not add materially to his work. The ecological approach to suicide has yielded results of interest to social medicine; an example is the recently completed work by Peter Sainsbury on suicide in London. Anthropologists have also contributed many interesting observations. Clinical psychiatrists have been concerned mainly with the relationship between suicide and mental illness, and with the prevention and prediction of suicide. The study of the psychopathology of suicide received a strong impetus from psychoanalysis. Freud's theory of the death instinct was accepted by the majority of psychoanalysts, and aggressive tendencies directed against the self have been studied in great detail (Menninger, 1938). The knowledge of suicidal equivalents or, as Henry Wilson (1942) called them, "suicidal compromises", was an important advance. Some students of the problem of suicide, Schilder (1942), Zilboorg (1936), and Masserman (1947), did not accept the theory of the death instinct. They were inclined to regard suicidal acts as perverted manifestations of the instinct of self-preservation. However this may be, our knowledge of psychopathology has been greatly enriched by the study of the mental mechanisms which enter into suicidal acts. But so far it has not enabled us to predict with any certainty what form self-destructive tendencies will take in individuals. One cannot escape the impression that research into the problem of suicide has been almost stagnant for some time. This, I believe, has been due to the preoccupation of the majority of research workers, psychiatrists and sociologists alike, with a retrospective analysis of people who had committed suicide. These post-mortems are only of limited value for clinical psychiatry. But we can learn a great deal through an intensive study of those who have survived suicidal attempts. It is astonishing how much we do not know about them although we meet them daily in our work. They are, probably, as a group, not the same population as those who actually commit suicide, but it would be very surprising if a study of that group did not also add to our knowledge of the other. Much has, of course, been written about attempted suicide, but most writers were concerned with exactly the same problems that had been studied in those who had committed suicide. This is not surprising, for most people, including psychiatrists, look on a person who has attempted suicide as somebody who has bungled his suicide. This is why the living are called unsuccessful and the dead successful.

There are many questions about attempted suicide to which one would very much like to know the answers. I will mention a few only. What is the relationship between the two populations: those who commit suicide and those who attempt suicide? What is the size of the latter group? What happens to those who attempted suicide? How many kill themselves later, and what types are liable to do so? How does the suicidal attempt affect the patient's mental state? If suicide has been motivated by inner conflict, what happens to that conflict? If it was motivated by a crisis in human relations, were these modified by the suicidal attempt, and if so, how? What is the effect of the suicidal attempt on the patient's group and what are their reactions to it? Sociologists have stated that suicide is due to social disintegration and isolation. Do these factors hold good for the suicidal attempt, and, if so, are they influenced by it? Some of these questions are of immediate practical interest for the clinician. The study of others might help us to understand the function of the suicidal attempt in our society.

Some Data on Suicide and Attempted Suicide in Greater London

The Statistical Branch of the Metropolitan Police District has a register of suicides and attempted suicides. Fig. 1 shows the yearly totals for each group per 100,000 of population (aged 15 and over) for the years 1936 to 1950. The attempted suicide rate follows the trend of the suicide rate fairly closely. Until 1948, the former was lower than the latter. As found elsewhere, more men than women committed suicide, while attempts were more frequent among women. The police figures showed a peak in the age group of 65 to 74 in men, and of 35 to 44 in women. There has been a change in the choice of methods in recent years, drugs being used much more frequently than before. Fig. 2 shows this very clearly. The picture seems at first sight very alarming. The use of drugs for suicidal acts had been on the increase since the end of the war, but 1948 brought a dramatic rise which was further accentuated in 1950. This is obviously related to the increased availability of sedatives since the institution of the National Health Service in 1948. Closer inspection of the figures reveals that the increased use of drugs, most of which were sedatives, for suicidal acts has had a remarkable effect on the relationship between the suicide rates and the rates for attempted suicide. While the latter, and the total for both groups, went up steeply, the incidence of suicide through drugs rose only very slightly (Fig. 2). The enormous increase of suicidal attempts with drugs resulted in registered attempts outnumbering suicides for the first time (Fig. 1). This graph also demonstrates that during the same period the total suicide rate dropped to the same low level as during the war. The cause for this apparent paradox is not far to seek; according to the Statistical Branch of the Metropolitan Police, "drugs proved the least effective method, and the steady post-war reduction of the percentage of successful suicides was due to the increasing commonness of their use", which has been associated with a decline in the use of other methods. Thus the National Health Service has, by unwittingly offering sleep for death, reduced the suicide rate.

Suicide rates do not, of course, tell the whole truth. However, there is reason to believe that the degree of inaccuracy of the official suicide rates is fairly constant and that they include the majority of suicides. As to the attempted suicide rate, there can be no doubt that only a small fraction of attempts come to the knowledge of the authorities. It is quite clear from everyday experience that suicidal attempts greatly outnumber suicides. Yet the official rates for attempted suicide are, as a rule, below, or only slightly above, the suicide rates. How representative the fraction that makes up the official rate is, we do not know. The fact that it shows a constancy similar to the suicide rate suggests that it may after all be an indicator of the fluctuations in the incidence of attempted suicide, but its usefulness is obviously much more doubtful than that of the suicide rates. There are no data about the real incidence of attempted suicide. The Statistical Department of the Metropolitan Insurance Company of New York, where suicide rates have been studied carefully over many years, has estimated that the number of attempted suicides is about six to seven times as high as that of suicides. This seems nearer the truth, though it is probably still rather conservative. It would mean that, in 1946, when the official suicide rate for Greater London was 722, the number of attempted suicides would have been about 5,000, which seems a gross underestimate for an urban population of 8 millions. The number of attempted suicides registered in 1946 was actually 696.

A Follow-up Investigation Carried out Jointly with Dr. I. S. Kreeger and Miss Nancy G. Cook

We set ourselves to investigate some of the problems concerning attempted suicide. We regarded as a suicidal attempt every act of self-damage inflicted with the intention of self-destruction. We decided to begin with a follow-up investigation of a series of patients admitted because of attempted suicide to St. Francis Hospital Observation Ward between February 1, 1946, and January 31, 1947. We should have liked to match this group with a comparable series of admissions to a general hospital in 1946, but this proved impracticable. The named observation ward serves South-East London, and has a yearly admission rate of about 1,300. 138 patients fell into our group. Our aim has been to trace and re-examine them, and to interview their relatives. We have tried to ascertain their state of health and the immediate and long-term effects of the suicidal attempt on their relationship to their environment. We have also tried to find out about their knowledge of the legal implications of a suicidal

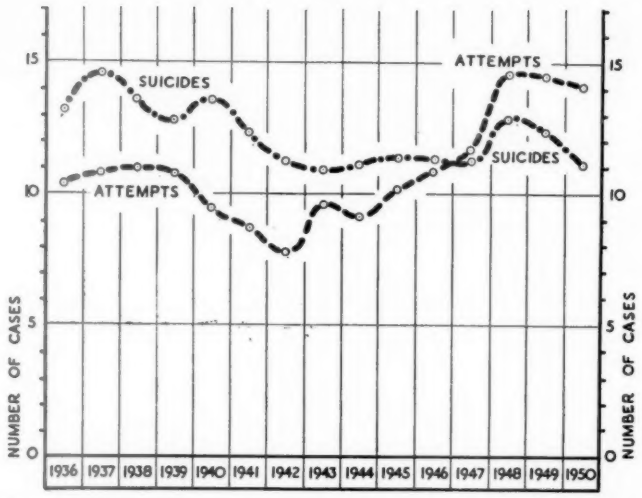

FIG. 1.—Yearly totals of suicides and attempts in Greater London, per 100,000 of population aged 15 and over. 1936–1950. Statistical Branch of the Metropolitan Police.

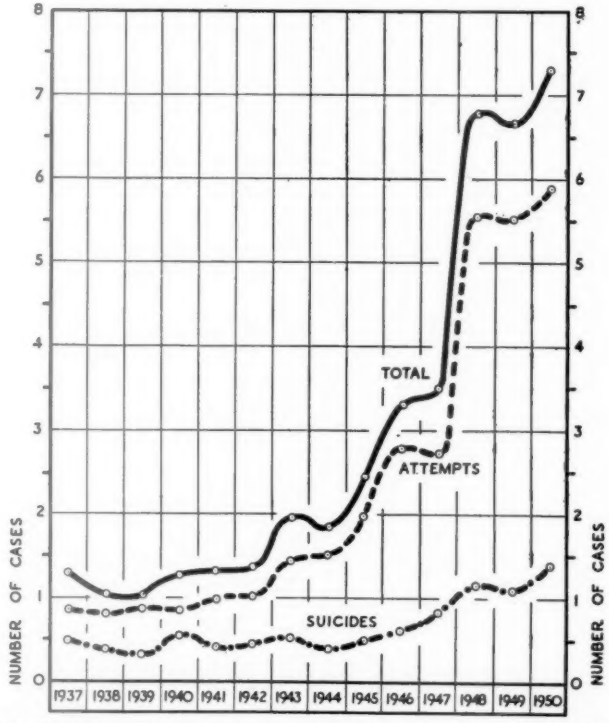

FIG. 2.—Yearly totals of suicides and attempts by drugs in Greater London, per 100,000 of population aged 15 and over. 1937–1950. Statistical Branch of the Metropolitan Police.

attempt, about their religious attitudes, and some other problems. Only a small proportion of patients were in a mental hospital at the time of the follow-up. The rest had to be traced and their co-operation and that of their relatives had to be won. They proved a very elusive group and we came to understand why such a follow-up had never been carried out before in this country. I wish to pay tribute to my co-workers who overcame difficulties which often appeared insurmountable.

Table I shows the sex distribution and the modes of admission of the 138 patients. Two-thirds were transfers from general hospitals. There were more men than women, which was at variance with the rule that more women than men attempt suicide. It is of interest that also in Hopkins' series (1937) of admissions for attempted suicide to an observation ward at Liverpool men outnumbered

138 PATIENTS ADMITTED TO ST. FRANCIS HOSPITAL OBSERVATION WARD BETWEEN FEBRUARY 1, 1946, AND JANUARY 31, 1947, FOLLOWING SUICIDAL ATTEMPTS

TABLE I.—MODES OF ADMISSION

	Men	Women	Total	%
Transferred from other hospitals	49	41	90	65·2
From Police	10	2	12	8·7
From Home	15	21	36	26·1
Total	74	64	138	

TABLE II.—DIAGNOSES

	Men	Women	Total
Group A.			
Schizophrenias	6	5	11
Man.-depr.: involv. depr.	18	25	43
Senile psychoses	6	4	10
Other organ. reaction types	6	2	8
Total	36	36	72
Group B.			
Psychopathic reaction	15	6	21
Neurotic depression	23	22	45
Total	38	28	66

TABLE III.—DISPOSAL

	Men	Women	Total
Discharged from observation ward	13	14	27
Transferred to mental hospitals	52	48	100
Transferred to general hospitals	3	1	4
Died in observation ward	6	1	7
Total	74	64	138

TABLE IV.—TIME FROM ATTEMPT TO DISCHARGE FROM OBSERVATION WARD OR MENTAL HOSPITAL. DEATHS IN HOSPITAL

	Discharged recovered or relieved	Died in hospital
Less than three months	76	12
Three to six months	14	1
Six months to one year	12	1
One to five years	5	7
Patients remaining in mental hospital	10	

TABLE V.—STATE OF GROUP AT TIME OF FOLLOW-UP

	Men	Women	Total
Total group	74	64	138
Dead			
Died within three months	12	2	14
Died from three months to five years (1 suicide)	13	8	21
Total	25	10	35
In mental hospitals			
Remaining since attempt	6	4	10
Following readmission	2	6	8
Total	8	10	18
Out of hospital	35	35	70
Probably alive, whereabouts unknown	6	9	15*

*This figure has been reduced to 11 since this paper was read.

women. In our group they were in the majority among the transfers from general hospitals and among those admitted through the police, but not among the direct admissions. Possibly the fact that suicidal attempts in men appear, as a rule, more dangerous, caused more men than women to be transferred for observation. 43 of the patients (25 men, 18 women) were known to the police as having attempted suicide. None of them was proceeded against.

Table II shows the diagnostic grouping. The preponderance of psychoses in this series is not surprising. Usually the proportion of psychoses among suicides and attempted suicides does not exceed one-third of the total number.

Table III illustrates the modes of disposal. Only 38 out of 100 went to a mental hospital under certificate. The number of patients who died in the Observation Ward was considerable. In 2 of them death could be regarded as a late indirect result of the suicidal attempt.

Table IV shows the duration of stay in hospital. After three months two-thirds had either left hospital or died. The comparatively high mortality rate of the group as a whole (*see also* Table V) was due to the fact that more than one-fifth were above 60. However, their mortality rate did not differ significantly from that of non-suicidal patients. We were fortunate in having a control group in Dr. Post's study (1951) into the mortality rate of aged patients admitted to the same Observation Ward. Our series, when divided into age groups, showed two peaks among the male patients (age groups 35–44, and 65–74), and one peak among the females (age group 25–34).

Table V shows the state of the whole group at the time of the follow-up. So far we have been able to establish death by suicide in only one patient. 15[1] could not be traced, but we hope to reduce this number still further. We assume that they are alive as their names could not be found on the register of deaths. We are aware of the fallacies of this assumption: they may have left the country or may have been registered under different names.

It is not proposed to discuss motives. Physical illness appeared to have been responsible for the suicidal attempt in 9% of our patients. The results of our investigations into the patients' attitudes to the legal implications of the suicidal attempt and to its religious aspects will be reported elsewhere. Social isolation was clearly an important factor. 22·6% of our patients were living alone when they attempted suicide, as compared with 5 to 6% among the general population. An analysis of the methods employed showed that 1 in 4 of our patients used drugs. Wounding and coal gas figured next on the list. The non-psychotic patients used drugs three and a half times more frequently than the psychotic patients. Women employed less dangerous methods than men. Attempts were most frequent in May. All this is in keeping with the observations of other investigators.

A question which is often discussed is that of the degree of suicidal intent or, as it is usually put, of the seriousness of the attempt. This is difficult to assess so long afterwards, and is much better studied in recent cases. But even so, the patients often fail to throw light on this question, because the way in which it is usually phrased implies that a genuine suicidal attempt ought to aim only at death—a thesis which we propose to challenge. If we care to measure the seriousness of an attempt by the degree of unconsciousness, or the extent of the injury inflicted, we find that this factor cuts across diagnostic boundaries. In some of the schizophrenic and depressive patients the threat to life was so small that, had they belonged to the neurotic and psychopathic groups, they could have served as typical examples for insincere or even faked attempts. And those were not the patients whose mental state would have made more serious self-injury impossible.

22 of our patients had a history of previous suicidal attempts. 18 made subsequent attempts, which in one case proved fatal. This was a man of 69 with hypertension and increasing deafness who had lived alone since his wife's death a year before. He had refused his sister's offer to look after him. Following an apparently trivial quarrel with her, he tried to kill himself with aspirin and gas, and left a note complaining that nobody wanted him. He was taken unconscious to a general hospital, and transferred to the Observation Ward. Here he appeared free from depression, and refused to go to a mental hospital. He was discharged under the care of friends with whom he was supposed to stay, but within three weeks he moved back to his own house. He gassed himself ten months after the first attempt. It emerged that some weeks before his death he had suffered a shock: his sister had divulged to him that his wife had often thought of leaving him. This patient did not take advantage of his chance, brought about by his suicidal attempt, of a fundamental change in his social situation. Perhaps the outcome would have been different had it been possible to keep him in hospital longer.

It would not be justifiable to generalize from the result of our follow-up. Our group is not representative of the suicidal attempts made in the general population. It is doubtful whether it will be possible to study a truly representative sample. The only way of reducing that disadvantage is to study several other groups. This we are trying to do. We hope, in the course of time, to give a more complete picture of the fate of people who have attempted suicide. The only systematic follow-up of suicidal attempts that I could find is that by Dahlgren (1945), carried out in the general and mental hospital at Malmö. His group consisted of 230 patients of whom the majority were women. He confined himself to establishing how many were still alive two to seven years later, and how many had recovered from their mental illness. He was interested mainly in statistical problems. His group differed considerably from ours. The proportion of psychoses was much smaller. Half his patients were alcoholics. (We have been able to ascertain only 6 alcoholics among our patients.) The loss through death by

[1] This figure has been reduced to 11 since this paper was read.

natural causes was very small. He found that 10 men and 4 women had committed suicide, all within four years. This should serve as a warning against the undue optimism that our results may encourage. Dahlgren's group cannot, however, be regarded as representative of suicidal attempts in an urban population. It is true that it included general hospital cases, and that the sex distribution was more typical of the attempted suicide group as a whole than it was in our series. But his material also has some flaws. The older age groups were under-represented. Further, it seems that the majority of Dahlgren's patients were either discharged immediately or kept in hospital for a short time only.

Observations we have made on another group of patients whose follow-up is in progress, together with the results of our series and of Dahlgren's study, suggest that a small proportion of those who have attempted suicide will finally kill themselves, their number largely depending on the reaction of their human environment to the suicidal attempt. This assumption is in keeping with the experience that in the histories of patients who died through suicide we sometimes find references to previous suicidal attempts; but they are only a minority of those who take their life. The majority of those who kill themselves do so at the first attempt. One may say that the two groups, the suicides and the attempted suicides, overlap slightly. I mentioned before that attempted suicides are usually regarded either as bungled suicides or as fakes. But are not some, or many, so-called successful suicides bungled attempted suicides?

It seemed worth while to look afresh at attempted suicide, this time as a behaviour pattern, without any preconceived ideas about its aim and biological significance. This we have done with a great variety of patients over the last eighteen months. It becomes obvious that self-destruction cannot be the main and only purpose of the suicidal attempt. The self-injury in most attempted suicides, however genuine, is insufficient to bring about death, and the attempts are made in a setting which makes the intervention of others possible, probable, or even inevitable. There is a *social* element in the pattern of most suicidal attempts. Once we look out for that element we find it without difficulty in most cases. There is a tendency to give a warning of the impending attempt, and to give others a chance to intervene. We remember how few suicidal attempts are carried out in circumstances that would make death certain. If we think in terms of a social field we may say that those who attempt suicide show a tendency to remain within this field. In most attempted suicides we can discover an appeal to other human beings. Psychopathological studies have shown that this particular appeal is also a powerful threat. If it is overlooked or remains unheard, or if it is smothered by the force of the self-destructive impulses, the suicidal attempt will "succeed". The outcome, therefore, depends on whether there is a receiver for the appeal. Sometimes he has to be shouted for. We regard the *appeal character* of the suicidal attempt, which is usually unconscious, as one of its essential features, but it certainly is not the only one that determines its purpose. If one had to design a pictorial symbol for attempted suicide one would present this act as Janus-faced, with one aspect directed towards destruction and death, and the other towards human contact and life. There is another fundamental feature in attempted suicide which may be called its *ordeal character*, the term ordeal being used here in its original sense, i.e. of an ancient trial in which a person was subjected, or subjected himself, before the community, to a dangerous test the outcome of which was taken as divine judgment. The so-called failure of a suicidal attempt is usually accepted without demur, at least for a time, and in a considerable number of patients the depression disappears immediately after the attempt. From the biological aspect we may regard the suicidal attempt as a catastrophic reaction to an intolerable social and emotional situation. Within this wide definition fall suicidal attempts to spite others, attempts which aim at reunion with someone who has died, and those outbursts of aggression against the self and the environment in the course of which the boundaries between them have temporarily become blurred.

Most of what I have said can be described in terms of psychodynamics, i.e. as the result of primitive urges and conflicts. Our studies confirm and complement many psychopathological observations and theories, especially those pertaining to the role of the aggressive tendencies in suicidal acts. However, on this occasion we prefer to describe the suicidal attempt in terms of behaviour in a social situation which can be observed without much difficulty once we have disabused our minds of the current but erroneous idea that the sole aim and biological purpose of the suicidal attempt is death. The story of that misconception, from which springs the common concept of the successful and the unsuccessful suicide, would make an interesting study in itself.

Effects of Suicidal Attempts on Human Relations

The suicidal attempt usually results in some modification of the individual's attitude to himself, and of his social situation. The response of the human environment is of decisive importance. The most obvious example is that of the patient who, as the result of a suicidal attempt, is taken into hospital, and remains there temporarily or permanently. His social position has been transformed fundamentally, irrespective of whether it has been his illness which had changed his relation to his environment, or whether he has become isolated through bereavement or other events in the group of which he was a member. For many patients, the suicidal attempt initiates a new era in their relationship to their environment, if only by enabling them to keep it constant while the inner world preoccupies

their thoughts and senses. In some of them, the suicidal act has been the last attempt at controlling their fate. But what happened to those who left hospital? What effect did the suicidal attempt have on them and their human relationships? In a group of our patients it was difficult to separate the effects of the illness which had culminated in the suicidal attempt, from the effects of the attempt itself which had served as an alarm signal. I am thinking mainly of patients with depressive illness; but in some the suicidal attempt left a mark which could not be accounted for by the illness alone. The reaction of the environment to a depressive illness with and without suicidal attempt tends to be different. To the patient the suicidal attempt stands for death, and survival, and a new beginning. To the relatives it stands for bereavement and mourning. It sometimes creates the peculiar situation in which somebody who has died and revived is with us alive while we are mourning him. All this engenders a tendency to renewal and revision of human relations on the part of all concerned. Those processes of readjustment in the social field are, of course, very obvious where an apparently clear-cut social situation had precipitated the attempt.

We found a number of typical developments. The following exemplifies one of them: A man of 33 was persuaded by his mother into marrying his girl friend who was pregnant by him. His attitude to the girl had been ambivalent and he had shown signs of anxiety for some time. This culminated in a state of panic amounting to confusion, and four days after the wedding he cut his wrists. He waited for death. When nothing happened he staggered to the police and was taken to hospital where G.P.I. was discovered. Six months later he was discharged recovered. He returned to his wife to whom he had gradually become reconciled while in hospital, and their relationship has remained satisfactory. Here the suicidal attempt had been an alarm signal. If there are suicidal attempts which deserve the epithet "successful", this was surely one of them.

There was a group in which suicidal attempts cemented crumbling relationships. Here it worked towards greater cohesion within the group. There were others in which it resulted in a rupture of precarious human relations. An example of this was a young man who, following a suicidal attempt, was finally rejected by his wife and her family and had to return to his mother. Here the suicidal attempt had resulted in a regression to a less mature state of human relations. This phenomenon of regression could be observed in a considerable number of patients. It usually was a return to a state of greater dependency. There were some other modifications in human relations which the suicidal attempt brought about. But they cannot be presented within a brief sketch and sometimes, of course, the suicidal attempt failed to change the life situation. In those cases the prevailing state of affairs was either accepted or the attempt was repeated. Sometimes suicidal attempts alternated with violence against others. These observations will be reported more fully in a joint publication.

There can be no doubt that suicidal attempts are very frequent. The cause for this lies partly in the attitude of our society. It is probably true to say that we can tolerate the threat of suicide of a member of our group less than any other threat, including that of murder. This gives the appeal character of the suicidal attempt such a tremendous force. It has probably not always been so. Perhaps we now feel much more that we are our brothers' keepers than people did at the time when life and death were more commonly regarded as the responsibility of a personal God than they are to-day. Moreover, a suicidal attempt may have less meaning for those to whom life and death are one continuum. It would be interesting to study attempted suicides in societies where life is not valued as highly as in ours. But there are, of course, periods in our society when this is so, i.e. the periods of war, when the rates for attempted suicide invariably decline. This is usually explained by the greater social cohesion that war brings about. But could not the decline in the value of life, and thus the loss in the force of appeal inherent in the suicidal attempt also be a factor? Whenever the appeal is likely to go unheard, attempted suicide becomes infrequent. This was so in the German concentration camps (Kral, 1951). In a hostile society the suicidal attempt has lost one of its main functions.

The research that I have reported here is only a pilot study to a more systematic investigation into attempted suicide. Our work has so far posed more questions than it has answered. Our follow-up studies are necessary for a general orientation as to the relationship between the suicide group and that of attempted suicides. We have satisfied ourselves that, from an epidemiological point of view, these are two different populations, but that there is a strong tendency on the part of certain members of the attempted suicide population to stray into the area of the other. It seems that it is in our power to reduce the number of trespassers to a minimum. But what about the trespassers from the other side? Among the attempted suicides there must be a number of thwarted suicides. How can one recognize them? Is it possible to differentiate clinically between the attempted suicide and the "bungled suicide"? Are perhaps the latter the ones who finally kill themselves? We hope that our investigations will throw some light on these problems. When we study them psychologically we find no boundaries between the two populations. Our observations on attempted suicides, and experience of suicides, suggest that the difference lies, not so much in variations in the force of the destructive impulses but in the degree to which conflicts have tended to become "internalized". This is a hypothesis that we hope to be able to test. Apart from helping us to formulate hypotheses, our investigations have given us interesting information, at least about our series of patients. I trust that our findings will not give rise to

undue optimism, and that inexperienced doctors, in dealing with individual patients, will not adopt the principle "Once an attempted suicide, always an attempted suicide"! In fact, our observations demonstrate the value of caution.

Lastly, if the appeal character is such an important feature of the suicidal attempt as we have made it out to be, is there not a likelihood that this powerful and dangerous appeal will be used more and more, especially in a society which has made every individual's welfare its collective responsibility? I think that this danger can easily be overestimated. "Attempted suicide" is a behaviour pattern which is at the disposal of only a limited group of personalities.

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REFERENCES

DAHLGREN, K. G. (1945) On Suicide and Attempted Suicide. Lund.
DURKHEIM, E. (1951) Suicide. (Transl.) The Free Press, Glencoe, Illinois.
HOPKINS, F. (1937) *J. ment. Sci.*, **83**, 71.
KRAL, V. A. (1951) *Amer. J. Psychiat.*, **108**, 185.
MASSERMAN, J. H. (1947) *Dis. nerv. Syst.*, **8**, 324.
MENNINGER, K. A. (1938) Man against Himself. London.
POST, F. (1951) *Brit. med. J.* (i), 436.
SAINSBURY, P. In Press. Quoted from Lewis, A. (1951) *Edin. med. J.*, **58**, 223.
SCHILDER, P. (1942) Goals and Desires of Man. New York.
Statist. Bull. Metrop. Life Insur. Comp., quoted from Oliven, J. F. (1951) *New Engl. J. Med.*, **245**, 488.
WILSON, H. (1942) *Brit. med. J.* (i), 9.
ZILBOORG, G. (1936) *Arch. Neurol. Psychiat., Chicago*, **35**, 270.

Section of Epidemiology and State Medicine

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Epidemiological Methods in Preventive Medicine

PRESIDENT'S ADDRESS

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THE title of this Presidential Address caused me some thought for although I knew what I wanted to talk about, it seemed advisable to let any prospective audience also know what was in my mind. You will remember the advice given by the sage to the young lecturer: Tell them at the beginning what you are going to say, tell them in the middle what you are saying and tell them at the end what you have said. It may be well, then, to define more fully and precisely the meaning of our title. The constitution of this Section of Epidemiology enjoins us to study endemic and epidemic diseases. Epidemic means literally "among the people", and an epidemic disease is defined by the Oxford English Dictionary as a "disease which is prevalent among a people or a community at a special time and produced by some special cause not generally present in the affected locality". Epidemiology may accordingly be defined as the study of disease as a mass phenomenon, the unit of observation being a group of people, not a single individual as in clinical medicine. The fuller, and often quoted, definition set down by August Hirsch in 1883 states that "epidemiology is a science which will give firstly a picture of the occurrence, the distributions and the types of the diseases of mankind, in distinct epochs of time and at various points of the earth's surface; and secondly will render an account of the relation of these diseases to the external conditions surrounding the individual and determining his manner of life".

There is no particular mention of infectious diseases in these definitions, and yet today many of us think of epidemiology as being concerned specifically with the study of diseases transmissible by a known or suspected viable agent. It is true that through the ages epidemiology has become particularly associated with the group of "communicable diseases", largely because these infections have been the most prevalent and disastrous of the epidemic diseases. But it is interesting to note what Dr. Babington, the first President of the Epidemiological Society of London, said in 1850, while cholera and typhoid, scarlet fever and diphtheria were still plagues in our land. "Epidemic febrile diseases", he said, "will no doubt be the subject of our chief study as being immeasurably of the most common occurrence and most fatal in their results; but we must not forget that there have in times past existed, and there may exist again, epidemic visitations of diseases of a nervous character, as for instance tarantism, the dancing mania, and other allied infections; of a hæmorrhagic nature as apoplexy which has been known to exist epidemically in Holland; and even of a cachectic nature as leprosy and scrofula, in which diseases the endemic character has occasionally passed into the epidemic form." There was, of course, no hint in those days that leprosy and scrofula might be due to some transmissible agent for this was still the pre-bacteriological era. A little later, in 1862, the Epidemiological Society defined epidemic as "including the diseases classified as zymotic or miasmatic; many local and constitutional diseases which at times assume an epidemic character; and certain endemic and indigenous diseases such as goitre, pellagra and beri-beri which are peculiar to regions and countries".

There seems to be, then, good reason for adopting a broader definition of epidemiology than has become associated in the minds of many of us, and indeed this more general connotation has already come into use for we read in our medical journals about studies on the epidemiology of hypertension and heart disease, peptic ulcer and cancer, accidents and suicides. However, lest I offend reactionary susceptibilities I have used the term "epidemiological method", since it is technique or methodology that shall be our main concern here. The term Preventive Medicine is used in an all-embracing sense to cover Social Medicine and the Public Health, and indeed medicine generally, for surely the objective in all our medical researches is towards ways and means for the prevention of disease.

THE EPIDEMIOLOGICAL METHOD

Advances in our knowledge of the prevention and treatment of disease have depended on three main methods of investigation—the clinical, the laboratory, and the epidemiological. The clinical method was concerned at first with careful observation by eye and ear and touch of the signs and symptoms in the ill patient, and led to a separation into different disease entities. Sydenham, Bellonius and other French physicians were among the pioneers in this field. Later, various tools like the

stethoscope and the clinical thermometer helped in more precise diagnosis and now the clinician uses a whole battery of ancillary aids. He has also developed, under the inspiration of men like Sir James Mackenzie and Sir Thomas Lewis, what is called clinical science or bedside pathology where the patient or human volunteer is himself the experimental animal.

I need not elaborate the contributions which the laboratory has made to medical knowledge. The approach here is that of the experimentalist, and the methods used have been many and varied. The starting point has often been a clinical observation which has led to a hypothesis and that in turn has been put to the test by planned experiment. Careful observation in experimental work has often led to new and unexpected discoveries in which there is less element of luck than is sometimes supposed, for it is the trained mind and observant eye that gets these "lucky breaks".

The epidemiological method is apparently quite different from the clinical and laboratory approach. It depends basically on the collection of data about a community and its environment, but as Wade Hampton Frost has said in his introduction to the reprinting of John Snow's two classical papers "epidemiology at any given time is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extends more or less beyond the bounds of direct observation. Such of these chains as are well and truly laid guide investigation to the facts of the future; those that are ill-made fetter progress. But it is not easy, where divergent theories are presented, to distinguish immediately between those which are solid and those which are merely plausible". That Snow was among the first to lay the chains well and truly—what has been called a "shoe leather" rather than an "arm-chair" epidemiologist—is indicated by his use of the spot-map, probably for the first time, to indicate the distribution of the cholera cases in the Broad Street district, and his later demonstration, by visiting every house where a case of cholera occurred, that the infection was being spread by one company's water supply and not by another supplying the same area (Table I).

TABLE I.—CHOLERA DEATHS—LONDON 1854

Southwark and Vauxhall water supply	71 per 10,000 houses
Lambeth water supply	5 per 10,000 houses
Rest of London	9 per 10,000 houses

This approach to medicine is not after all so different from the clinical approach where the ill-made chain of inference based on careless or inadequate observations easily leads to erroneous diagnosis, whereas the experienced diagnostician who has developed a thorough method of examination, supported if need be by ancillary aids, is much less likely to make mistakes.

History supplies numerous examples of mistakes in epidemiological diagnosis, particularly in the days when the collection of data was rather haphazard and there was little appreciation of the need for controlled statistical analysis. There was the famous controversy, in which Noah Webster, the father of the dictionary, took an active part, as to whether yellow fever in Philadelphia was a native or an imported disease. Even the "great sanitary awakening" in the last century was based on an erroneous conception of the relationship between dirt and disease. It was because of John Snow's infinite capacity for painstaking observations and for critical analysis of the marshalled data that Frost developed such an admiration for him, and Frost himself, perhaps more than anyone else, has helped to transform epidemiology from a speculative philosophy to an analytical and productive science. I would recommend to any budding epidemiologist that he read carefully through the Papers of Wade Hampton Frost (1941) and he will find there the most practical demonstrations of the development of epidemiological concepts and methods.

The basis of all epidemiological enquiry is of course the vital statistics supplied by the practitioner and the Medical Officer of Health and analysed by the Registrar-General. The collection and dissection of vital statistics is, as Ryle called it, social pathology and we may be proud that the development of biostatistics has been led so ably by pioneers in this country—I need mention only John Graunt with his London Bills of Mortality, William Farr who supplied the ammunition for John Simon and the other public health reformers of the nineteenth century, Francis Galton and Karl Pearson who introduced new statistical tools or sharpened the old ones, and in our own time such stalwarts as John Brownlee, R. A. Fisher, Major Greenwood and Bradford Hill.

The social post-mortem examination, like the individual autopsy, depends on team work; on the one hand the clinician, the morbid anatomist, bacteriologist, biochemist, &c.; on the other, the practitioner, M.O.H., the statistician, the mathematician and so on. But the objectives are quite different; in the individual case, post-mortem analysis leads to better diagnosis and better treatment; in the community, social pathology leads to epidemiological enquiry and public health measures to prevent or control disease. The two methods are not mutually exclusive; many of the older clinicians were also good epidemiologists. But the modern physician becomes so engrossed in the complicated minutiæ of diagnosis and treatment of disease in the individual patient that he has no time for the broader issues. John Ryle changed from clinical to social medicine because he felt that the medical profession was becoming less surely attuned to some fundamental human needs—the deeper personal needs of the individual and the broader social needs of the community. Fortunately, we have a small but growing band of clinical workers who are carrying on the torch.

Medical Ecology

Epidemiology, then, by our broader definition, is concerned with all the factors contributing to mass disease, and these factors may be considered under three components—the ætiological agent, the host and the environment. This approach to disease in the community might be called medical ecology.

Thus, in studies on tuberculosis, we no longer think of the tubercle bacillus as being *the* cause of the disease; it is one of the causes with host resistance and environmental conditions playing a major role in determining the severity of the clinical infection. Besides the more obvious parasitic or biological agents of disease, there may be physical or chemical agents in extremes of heat and cold, tools causing mechanical injury, chemical poisons like lead and arsenic, deficiencies of hormone activators and vitamins like iodine and niacin.

The host's reaction to the ætiological agent will vary according to his inherent or natural resistance on the one hand and his acquired resistance on the other. Race, age, sex, heredity, nutrition, &c., all play their part. Tuberculosis behaves quite differently in the white and coloured races. Measles is a disease of early childhood in most countries since children are highly susceptible to the virus, but after the attack maintain a high resistance for life. Young children are much less susceptible to the typhoid bacillus so that typhoid fever is a rare or atypical disease in early life and is seen in its characteristic form in adults. The concept of infection as a host-parasite relationship in which both parties are primarily concerned to go on living and multiplying, has been developed by such protagonists as Theobald Smith and Burnet, and is now well established in bacteriological teaching. As a rather complex example, in talking of typhus, I tell the students of Zinsser's plea that we shed a tear for the apparent villain of the piece, the poor louse which, in conveying the rickettsia from man to man, suffers a 100% mortality while we escape much more lightly.

In like manner host resistance to disease will be affected by anatomic, metabolic and mental derangements. Nutritional status may determine the incidence of fractures and rickets which are much less common than half a century ago, whereas the stress and strain of modern life is apparently associated with an increasing incidence of peptic ulcer and cardiovascular disease, and the occurrence of motor-car accidents has been shown to have a direct relationship to the mental state of the driver.

Besides recognizing this interrelationship of ætiological agent and susceptible host in the disease process, the epidemiologist is very cognizant of the effect of environment as a contributory factor. Environment is a composite of many elements. The physical effect of climate and weather on the seasonal and geographic distribution of many diseases has long been recognized. Hippocrates in his great epidemiological treatise "Airs, Waters and Places," tells us that "hot winds cause poor appetite, derangement of the digestive organs, flabby physique: in man they lead to dysentery, diarrhœa and the ague with pleurisy and pneumonia rare. Cold winds make men sinewy, spare and costive: they conduce to pleurisies and acute diseases".

We have come to accept the seasonal distribution of the respiratory and intestinal infections as commonplace, but have we enquired enough into the manner in which these climatic factors operate, and have we studied sufficiently the effect of the individual components that make up climate—temperature, humidity, wind velocity, rainfall, sunshine and fog? Why, for example, is the young child's resistance to respiratory infection so markedly affected by sudden drops of temperature, and why are typhoid fever and poliomyelitis autumnal diseases in countries with temperate climates? In this last connexion, the recent epidemiological researches of Armstrong (1950, 1951) on the relationship of humidity to the incidence of poliomyelitis are very interesting and suggestive. Armstrong's thesis is that respired air is warmed to a temperature around 90° F. and through absorption of moisture from the upper respiratory mucosa, its relative humidity is raised to approximately 90%. When cool, dry air is breathed, the mucosal secretions may be stimulated and dried and in this way interfere with the establishment of poliomyelitis virus which in his view has its infective reservoir in the upper air passages. When warm, moist air is breathed, there is no such hindrance to the entrance of the virus. Examination of the seasonal incidence by weeks or months of an outbreak of poliomyelitis in the Washington area in 1950 showed a remarkable correlation between peaks of incidence of the disease and variations in the relative humidity of the air warmed to a temperature of 90° F. with a lag period of two to three weeks in the occurrence of the poliomyelitis cases which would correspond with an incubation period of seven to fourteen days. It was further shown that only after the relative humidity of the air, warmed to 90° F., rose above 27–28% in June did cases of poliomyelitis begin to occur, and there was a rapid fall in incidence three weeks after the humidity fell below this level in October. Armstrong therefore suggests that it may be possible to predict some weeks ahead the occurrence of an outbreak of poliomyelitis, if it is known that the virus is already present in a susceptible community.

I may, perhaps, be allowed to mention here a prophecy of a rather different kind. Dr. John Gordon of Harvard has told me that when he talks to his Public Health class in November he always warns them to look out for an epidemic of automobile accidents on or about a certain date in December; for around that time the first fall of snow invariably comes to Boston and the treacherous roads, plus the unprepared drivers, precipitate a marked increase in the accident rate.

Besides the climatic factor, there are usually also biological and social components in the environmental contribution to disease. On the biological side we must consider the whole economy of plant and animal life. The potato blight in Ireland had disastrous effects on human life and health, and rice famines have decimated by disease whole communities in India and China: even the present-day outbreaks of fowl-pest and foot-and-mouth disease could seriously curtail our limited supplies of protein. Plants, animals and insects may also act as reservoirs of infectious agents that are injurious to man. The epizootic of rat plague that precedes the human epidemic is well known to us, while malaria is being stamped out most efficiently in many lands, not by a direct attack on the parasite but by extermination of the intermediary host, the anopheles mosquito. Bovine tuberculosis and brucellosis in man are dependent on infection in the domestic cow and goat; vermin not only make inroads on our food supplies but also spread various diseases among us.

It is, however the social component of environment which has come under particular scrutiny in recent years. We have long known of the association between poverty and certain infections like tuberculosis and bronchopneumonia and the influence which social class has on the mortality rates of common childhood fevers like measles and whooping cough. But the factors within this component, social environment, embrace not only housing and clothing and food but also education, parental care, work and leisure and the whole way of life. Many of the prevalent diseases of to-day are linked to the social background; peptic ulcer, cardiovascular disease, chronic rheumatism, the visceral neuroses, psychosomatic disorders and accidents all have social components in their ætiologies, although these ætiological factors have not yet been sufficiently emphasized or analysed.

The point to be stressed is that most diseases have a plurality of causes, and the epidemiological method of enquiry is concerned to determine the relative importance of these various causative factors in a particular disease. In some instances, the agent of disease may be the most important factor as when a particularly virulent variant of the influenza virus wipes out thousands of our healthy young adults: or lowered host resistance may allow a less virulent strain of the virus to take a heavy toll of life as happened among the old populations of Liverpool and Southport in 1950. Or the complex environmental factors may play the predominant role as Villemin long ago recognized was the case in tuberculosis and as we are learning about many of our modern ailments. These various components of disease have a relative and varying weight which needs measurement and this is the function of the epidemiological method which is primarily concerned with ætiologies.

Epidemiological Dynamics

Disease in a community, like disease in the individual, is a dynamic not a static affair. It also, like individual disease, shows a gradation in its departure from the normal or healthy state. But it is just as difficult to define a healthy community as it is to define a healthy person. Obviously, we must base our standard of health on observations made on a reasonable number of apparently normal persons or communities. The resultant will not be a superman or a wholly healthy community but it will serve as a standard or control, against which we can measure abnormal or disease processes. Similarly, this standard will be the yardstick against which particular efforts towards the prevention or control of disease can be measured.

As an example, it would be generally agreed that in any modern civilization a sizeable proportion of the community will develop and probably die of malignant disease. But if some readily recognizable cancer, like that of the breast, is diagnosed and treated early, it might be hoped thereby to reduce the deaths from this particular cause. With that in mind, a number of health authorities, e.g. the State of Massachusetts and the Province of Saskatchewan, have embarked on large-scale and expensive campaigns for the early recognition and cure of accessible cancers, and are claiming good results from their efforts. McKinnon (1952) has, however, critically examined their statistics and has assessed the mortality rates in these states against those of other states and countries which have not adopted extensive cancer campaigns. His analysis indicates that the mortality rates from breast cancer in the different age groups show identical trends in the different states and countries from which comparable statistics are available. This does not mean that we should relax our efforts to recognize and treat cancer as early as possible but it does indicate that the more malignant breast cancers metastasize early and that the public may be misled about the value of propaganda for cancer control.

The biological gradient.—Just as health is compounded of a range of degrees of health, so most morbid processes show a gradient in the degree of severity—what Gordon (1950) calls the "biological gradient". We see it best, perhaps because we have studied it most, in the infectious diseases. The gradation from the characteristic clinical infection through mild, atypical forms to symptomless carriers of the infecting pathogen is well recognized but even in infections where most of the susceptible community suffer clinical attack, as in measles and whooping cough, we can see this biological gradient. If this gradient is carefully measured in the natural disease, we can assess the value of any prophylactic procedure, for example gamma globulin or pertussis vaccine, by the way in which it alters the gradient. Thus, in the whooping cough vaccines trials sponsored by the Medical Research Council, two groups of children whose average age was one year and who in other respects

were remarkably identical, were compared as to the incidence and severity of whooping cough over a period of two and a quarter years following vaccination. The vaccinated children showed a ratio of about 4 : 1 completely protected compared with the control group but in addition the biological gradient of the infection among those vaccinated was quite different from that of the natural infection (Fig. 1).

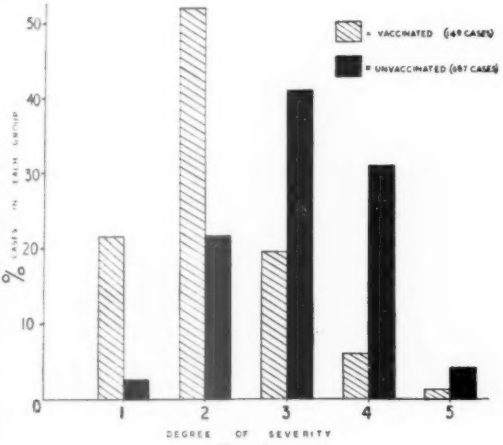

FIG. 1

MAJOR "REASONS FOR CHRONIC INCAPACITY" IN INSURED PERSONS : SCOTLAND 1936.

INSANITY	21·2
RHEUMATISM	12·6
DISEASES OF THE CIRCULATION	11·4
TUBERCULOSIS	11·2
BRONCHITIS	7·9
NEUROSIS	6·9
OTHER RESPIRATORY DISEASES	3·9
INJURIES	3·4

TABLE II

FIG. 1.—Severity of pertussis in vaccinated and unvaccinated cases. 1 = an abortive attack, with or without occasional paroxysms confirmed bacteriologically. 2 = fewer than 10 paroxysms in twenty-four hours at height of disease. 3 = 10–20 paroxysms in twenty-four hours at height of disease. 4 = more than 20 paroxysms in twenty-four hours at height of disease. 5 = attack complicated by bronchopneumonia, atelectasis, &c.

The same difference was seen in the studies of diphtheria among immunized and unimmunized communities reported by Hartley and Tulloch (1950). Indeed, it seems likely that this gradient is a common biological phenomenon in most diseases and careful observation of its characters in the natural disease will help to assess the value of any control measures. This is essentially the method of approach in the controlled clinical trials of new medicaments (*see* Hill, 1951), which has become common practice here and which, incidentally, is the envy of our American cousins.

Prevalence v. *Incidence*.—I should like to mention another dynamic factor in mass disease which sometimes leads to confusion. It is the difference between the *incidence* and *prevalence* of a disease. Incidence measures the rate of occurrence of new cases of a disease in a period of time, usually a year; prevalence expresses the frequency of existing cases of the disease at a prescribed time. Thus, a mass X-ray survey might discover approximately the same proportion of cases of pulmonary tuberculosis among the white and coloured populations of an American community but notifications of new cases and deaths would indicate that the incidence of pulmonary tuberculosis was relatively much higher in the negroes among whom the disease often runs a fulminating course.

With modern chemotherapy, which saves but may not cure patients who used to die of a progressive tuberculous infection, an increased prevalence of tuberculosis may be noted, although incidence, i.e. the occurrence of new cases, may be declining. So it is with other diseases like diabetes and pernicious anæmia where specific therapy prolongs life and leads to a greater prevalence, but not a higher incidence, of cases in the community.

Causes of death.—The dynamics of mass disease also leads to changes in the principal causes of death, and so reorientates our views about control or preventive measures for improvement of the public health. In 1901, the Captain of the Men of Death was pneumonia and bronchitis, which together accounted for approximately 82,000 deaths: there followed, in order, tuberculosis, heart disease, cancer and cerebral vascular disease. In 1949, the acute respiratory infections and tuberculosis had dropped to fourth and fifth places respectively and were superseded by the other three main killing diseases in the same order as in 1901 (Logan, 1950). The phenomenal decline in deaths from infectious diseases, which in the past half-century have fallen by 94%, has thus served to focus attention on cardiovascular disease and cancer, although we should remember that these are, for the most part, diseases of the older generation who have already made their contribution, and whose lives are less valuable than those of a younger age group. In this respect, tuberculosis, although it has fallen to fifth place as a cause of death, is still a most costly disease to the community because it causes a chronic and often fatal illness among men in the prime of life.

The changing nature of disease and the size of the problem which different diseases present may also be gauged from the register of chronic sickness which was kept as part of the pre-war Scottish morbidity statistics among insured persons, and which, it is hoped, may emerge again under the certification schemes of the Ministry of National Insurance. The Scottish figures for all workers aged 16 to 65 who had been on the sick list continuously for one year or more put insanity at the top, with rheumatism, circulatory diseases, tuberculosis, bronchitis, neurosis, other respiratory diseases and injuries following in that order (Table II).

The psychosomatic element is well represented in this list and it may be worth remembering Halliday's (1949) dramatic representation of the rise in the incidence of these diseases, while the more purely physical ailments declined in incidence and severity.

Applied Epidemiology

With the Registrar-General and the Minister of National Insurance as our guides, the application of the epidemiological method to problems of mass disease follows a basic plan which, of course, will be varied for individual needs. It involves, in order, a study of the nature and extent of the problem; a search for the causative factors of the disease and its peculiar distribution in the affected population; formulation of measures for prevention or control based on demonstrated ætiological factors; and, lastly, statistical evaluation of the results of control measures. In some diseases, rational control measures can be instituted before the agent of disease is precisely known, as Snow showed in his cholera studies and Goldberger in his pellagra investigations; in others, even when the factors of causation are defined, the application of control measures may present great difficulties if the habits and way of life of a community are not to be disrupted.

I do not propose to discuss in detail the epidemiological techniques by which these various steps are put into practice. It is essential that we should decide, as precisely as possible, what are the questions to which we want to find the answers; and it will usually be advisable to limit the questions and the variables so that the answers will be fairly clear cut. For example, we have lately begun a study of the ætiology of bronchitis and bronchopneumonia among young children in the Paddington area; and since overcrowding seemed likely to be an important causative factor in the complex environment of "poverty" we have designed our investigation to find, if possible, what part overcrowding specifically plays in the respiratory infections of infancy.

Perhaps we can best indicate the application of the epidemiological method by taking examples from different groups of disease; the communicable infections, the organic non-infectious diseases, the psychosomatic disorders, and accidental injuries.

Whooping cough.—In the first group whooping cough may be cited. Detailed studies such as those of Percy Stocks and Karn (1932) in four London Boroughs showed that 40–50% of children had had a clinical attack of this protracted debilitating infection by the age of 5 years and other information indicated that 70% of children aged 11–12 entering our Public Schools had been affected (Schools Epidemics Committee, 1938). Mortality figures showed that the infection was most severe in infancy and that death-rates were much higher in the lower than in the higher social grades, possibly because of secondary infections. There was good evidence that the agent of disease was the *Hæmophilus pertussis* which with careful cultivation on artificial media could be prevented from deteriorating into a rough non-virulent form. What was in doubt was the capacity of vaccines of this bacterium to give protection against whooping cough. The Medical Research Council therefore decided to test the prophylactic value of different vaccines on large and homogeneous groups of highly susceptible volunteer children, half of whom would be given injections of a control vaccine which could not give any specific protection against this disease. All the children were to be carefully observed for at least two years, the observers would not know which child had received pertussis vaccine and which the dummy vaccine, the severity of any clinical attack was to be graded and clinical diagnosis was to be corroborated by laboratory aids. The analyses of the first trials have been published (Medical Research Council Investigation, 1951) and show that the two groups of inoculated children were remarkably alike, that vaccination considerably affected both the attack rate and the severity of the infection, and that some vaccines were more effective prophylactics than others.

Lung cancer.—The phenomenal increase in the number of deaths attributed to cancer of the lung in the past thirty years has attracted great attention and stimulated many enquiries as to its reality and causation. Some hold that the increase is more apparent than real, being associated with a greater awareness and improved methods of diagnosis of the condition. On the other hand, Stocks (1947) has adduced convincing statistical evidence of a real increase. Between 1921–30 and 1940–44, the deaths from lung cancer among men at ages 45 and over had increased sixfold and among women of the same ages approximately threefold. Similar increases have been noted in other countries. Hypotheses about the causes of the increase (apart from better recognition) have centred round two main factors, (1) atmospheric pollution from car exhausts, tarred roads and the like, and (2) the smoking of tobacco. The study by Doll and Hill (1950) of the part which smoking may play is a good example of the application of the epidemiological method. The investigation was centred round

20 hospitals in the London area which were asked to notify all cases diagnosed as cancer of the lung, stomach, colon and rectum. These patients were then interviewed by almoners with particular reference to their smoking habits. For each lung cancer patient a non-cancer control patient of the same sex and age group in the same hospital was similarly interviewed at the same time. There were thus two control groups—one of patients with cancer of the alimentary tract, and one of non-cancer patients, which turned out to be strictly comparable with the lung cancer group except for some difference in the places of residence. Analysis of the data pertaining to 649 men and 60 women with lung cancer showed that 0·3% of the men and 31·7% of the women were non-smokers compared with 4·2% and 53·3% in the control non-cancer group. Among the smokers, 26·0% of the male cancer cases and 14·6% of the females were heavy smokers (25 or more cigarettes per day), compared with rates of 13·5% of the male controls and none of the females. There was thus a definite shift towards a heavier consumption of tobacco as cigarettes among the lung cancer patients. The possibilities that the results obtained might have been associated with an unsuitable control group, with bias on the part of the cancer patients about their smoking habits, or bias on the part of the interviewers were all critically considered and rejected. The conclusion was reached that smoking is an important factor in the ætiology of lung cancer.

The drawback to enquiries of this kind is that they are "looking back" rather than "looking forward" investigations, and Professor Bradford Hill is rightly extending the scope of this study by obtaining the smoking histories of a group of the population—the medical profession—scattered throughout the country; he now patiently, or impatiently, waits in his office to see which of us is going to die of lung cancer.

Peptic ulcer.—Peptic ulcer is a generic name for acute or chronic ulcerations of the gastric or duodenal mucosa, which has shown amazing fluctuations in its incidence and sex distribution in the last half-century. Evidence about its changing incidence and ætiology has been sought from many sources; mortality statistics, hospital clinical and autopsy records, population surveys, &c. As an example of the most satisfactory method of approach, the "forward-looking" population survey, I would commend the study of Doll and Avery Jones (1951) which makes full use of epidemiological techniques. Interesting points which emerged from the investigation were that in London 5·6% of men between the ages of 16 and 64 and 1·9% of women of the same ages have peptic ulcer; that the total number in England and Wales is around one and a half millions; and that incidence increases with age, reaching a maximum of 9·6% in men at ages 45–54 and 6·1% in women over 55. The sex ratio, men to women is 4·5 : 1 up to age 55 and after that 1·4 : 1. The expectation of developing an ulcer is almost constant, and at its maximum of 3·2 per 1,000 men, at ages 35–64, but gastric and duodenal ulcers behave differently in regard to age of onset. There is no support for the view that duodenal ulcers develop most frequently in young men.

Social class did not influence the incidence of duodenal ulcer but the occurrence of gastric ulcer was two-thirds less than expected in social classes 1 and 2 and two-thirds more in the lowest class, 5. As for peptic ulcer being an occupational disease, a high incidence among doctors was thought to be largely artificial because of refinements in diagnosis while there was no evidence of increased prevalence among 'bus or lorry drivers, shift workers or other occupational groups with the possible exception of foremen and business executives. There was a significantly low incidence among agricultural workers.

Anxiety over work, but not home worries, was an ætiological factor, but it may be that this anxiety is associated with a particular personality, i.e. the over-conscientious, hardworking, ambitious type of man who is said to be prone to peptic ulcer. You may say that many of these findings were already known to us but surely it is better to base our knowledge on observations backed by statistical analysis rather than on vague clinical impressions. Besides, studies of this kind point the way for further investigations into ætiology and towards preventive measures.

Automobile accidents.—Deaths from violence, which include accidents of all kinds but not suicides, have *not* increased in incidence in the past fifty years. Accidents are divisible into three groups—accidents in the home, on the roads, and in industry; although accidents on the roads have increased, accidents in the home, particularly burns and scalds, and accidents in the workshops have declined in incidence. With the exception of the enquiries into the ætiological factors in burns by Colebrook and others, the medical profession in this country has given little attention to the epidemiology of accidents, and we owe a debt to Gordon (1949*a*, 1949*b*) at the Harvard School of Public Health for showing us that the epidemiological approach to injury as well as to disease will lead to better understanding of ætiology and to rational preventive measures.

Accidents, of course, constitute one of our most serious economic problems, not only from the high proportion of deaths in school children and young men among whom death from violence is now the principal killer, but because of the temporary and sometimes permanent disability that results from the non-fatal accident. Accidents on the road nowadays take a high toll of limb and life, and it seems likely that epidemiological analysis would tell us a great deal about the causative factors and lead to better methods of control.

In Massachusetts, the high automobile accident rates associated with special holidays were analysed. Accidents were found to be twice as frequent in the early evening as in the morning although the same number of vehicles were involved. Certain roads and streets were found to have the highest rates. Police officers were therefore concentrated at these points at the material times, and as a result the holiday accident rate was reduced to a low level. Again, analysis of accidents according to the age of the driver showed two bulges in the curve, one in the age group 20–24 and the other in the advanced age group. In the first of these the accidents were associated with the male sex and when, instead of fines, the police authorities took more stringent measures against the foolhardy young men by withholding the driving licence for three to twelve months, the early bulge in the curve disappeared. Surely, this is epidemiology applied to the preservation of the Public Health.

In this country, the investigations into accidents in industry by the Industrial Health Research Board have included a study on accident proneness among motor drivers (Farmer and Chambers, 1939). It was found that men who had three or more accidents in their first year of driving buses had the same high accident rate five years later, while men with a low accident rate in their first year maintained their good record. Accident proneness could be predicted on the basis of certain psychological tests so that by utilizing these tests plus the performance in the first year's driving, unsuitable drivers could be diverted to other work and the accident rate reduced. It was also shown that accidents decreased with the age of the driver from 20–50 years, but showed a bump in the 50–60 age group when presumably advancing age and retarded reaction come on us imperceptibly and we still take the same risks as we did in our earlier years.

Conclusion

If I have neglected to tell you in the middle what it was I was saying, let me tell you at the end what I have tried to say. My thesis is that application of the epidemiological method is as likely to lead, and has already led, to just as important advances in medical knowledge and control of disease as result from the use of the clinical and laboratory methods. Progress in this field can be confidently predicted, since the past ten to fifteen years have seen great advances in the scope, the methods and the tools of epidemiological enquiry.

The epidemiological method is primarily directed towards ætiology, which may concern the agent of disease, the host and the environment, and the results obtained are applicable to an improvement of the public health by preventive rather than curative measures. Indeed, the epidemiological method may lead to rational control measures before the agent of disease is precisely known, as John Snow demonstrated when he persuaded the Board of Guardians to remove the handle of the Broad Street pump thirty years before the cholera vibrio was known, as we might to-day advise the Government that heavy cigarette smoking is a dangerous habit although we do not yet know its precise relationship to cancer of the lung.

REFERENCES

Armstrong, C. (1950) *Amer. J. Publ. Hlth.*, **40**, 1296.
—— (1951) *Amer. J. Publ. Hlth.*, **41**, 1231.
Doll, R., and Hill, A. B. (1950) *Brit. med. J.* (ii), 739.
——, and Jones, F. A. (1951) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 276.
Farmer, E., and Chambers, E. G. (1939) *Rep. Industr. Hlth. Res. Bd., Lond.*, No. 84.
Frost, Wade Hampton (1941) Papers of Wade Hampton Frost, Commonwealth Fund, New York.
Gordon, J. E. (1949*a*) *Amer. J. med. Sci.*, **217**, 325.
—— (1949*b*) *Amer. J. Publ. Hlth.*, **39**, 504.
—— (1950) Tomorrow's Horizon in Public Health, New York.
Halliday, J. L. (1949) Psychosocial Medicine. London.
Hartley, P., Tulloch, W. J., *et al.* (1950) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 272.
Hill, A. B. (1951) *Brit. med. Bull.*, **7**, 278.
Logan, W. P. D. (1950) *Popul. Stud.*, **4**, 132.
McKinnon, N. E. (1952) *Surg. Gynec. Obstet.*, **94**, 173.
Medical Research Council Investigation (1951) *Brit. med. J.*, i, 1463.
Schools Epidemics Committee (1938) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 227.
Stocks, P. (1947) *Stud. med. Popul. Subj.*, No. 1.
——, and Karn, M. N. (1932) *J. Hyg. Camb.*, **32**, 581.

Section of Radiology

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Cysts of the Lung

By THOMAS LODGE, M.B., F.F.R., D.M.R.

THIS subject of "Cysts of the Lung" is a somewhat recondite one which would certainly have been of less interest, incidence and importance but for the development of mass radiography. My purpose in the present communication is to discuss cysts of the lung either single or multiple rather than cystic disease of the lung.

The word "cyst" is as old as spoken language. The term was used to describe parasitic cysts 5,000 years ago. A cyst is defined by Muir (1941) as a space containing fluid and lined by endothelium or epithelium. This definition might be improved to read as follows:

"A cyst is a pathological space containing fluid or semi-fluid and lined by epithelium or endothelium"—and for the purpose of this paper, I would like to extend the definition still further to include air-filled spaces lined by epithelium or endothelium.

A cyst occurring in the lung may be expected therefore to be lined by the only type of epithelium constantly found in the lung, namely, bronchial epithelium, which is commonly columnar and may be ciliated, depending on its position in the bronchial tree. But a cyst occurring *in* the lung is not necessarily *of* the lung in so far as its epithelium is concerned and it should be remembered that almost any tissue may, during minor aberrations of development, be included within the lung and subsequently itself develop in the direction of cyst formation, for example, cysts of enteric origin. Further, the enclosed localized manifestations of parasitic disease are also cysts, and the term has been further extended to include certain results of injury as "traumatic cysts".

History.—This is well summarized by Conway (1951). From Fontanus (1638) onwards most accounts were based on the discovery of cysts post-mortem in young subjects, notably infants and children. In 1925 Koontz reviewed all the existing accounts and then Schenck (1937) made an analysis of the 374 cases published up to that time.

It is significant that the growing spate of recorded cases from 1938 onwards parallels the expansion of mass radiography services, an indication that pulmonary cysts are, in the main, not associated with symptoms.

Pathogenesis.—For centuries, lung cysts have been regarded as invariably or predominantly of congenital origin in the sense that the primary cause is a local aberration of development during intra-uterine life. Contributory factors to this conception were probably the frequent finding of cysts in infants and children and the occasional co-existence of true developmental anomalies, the best example of which is the association of cystic bronchiectasis with transposition of the viscera in Kartagener's syndrome.

This concept was accepted by Rizzi and de Lorenzi whose monograph (1948) is the most complete and authoritative work on the subject. They therefore divided all lung cysts into *Parasitic* and *Congenital* types (Table I).

TABLE I.—CLASSIFICATION OF LUNG CYSTS (*According to Rizzi and de Lorenzi*)

(*a*) *Parasitic*		(*b*) *Congenital*	
Hydatids	Cysticercus	A. Dermoid	F. Cholesterin cysts
Pulmonary mycoses	Coccidiomycosis	B. Thymic	G. Œsophageal (or gastric)
		C. Branchial	H. Pericardial origin
		D. Thyroid cysts	I. Pleural origin
		E. Lymphatic	J. Sero-mucinous cysts

Sero-mucinous cysts (arising from respiratory or intestinal elements or both) form 23% of all lung cysts (according to Schenck).

A congenital developmental origin once having been assumed, the way was clear for theories on the actual mechanism and these theories are legion, but can be grouped under four main headings:

I. Malformation

(*a*) *Of Respiratory Elements*

(i) Localized stasis or slowing of bronchial development.
(ii) Excess of formative tissue (King and Harris, 1937).
(iii) Dysontogenesis (prenatal, producing bronchial cavities).
(iv) Isolated mass of cells which canalize and secrete.
(v) Independent epithelial disorganization giving rise to cysts.
(vi) Malformation with dislocation of bronchial territory.
(vii) Altered embryology of bronchi.
(viii) Bronchial hypergenesis with a supernumerary bronchus.
(ix) Cystic dilatation from dysplasia of a peripheral bronchus.

(*b*) *Of Intestinal Elements*

(i) Anomalies arising during division of the primitive foregut into anterior (or pulmonary) and posterior (or œsophageal) parts with intestinal inclusions in the pulmonary part.
(ii) Dysontogenesis. The cephalic end of the alimentary canal can evolve in a respiratory fashion according to Bert and Fisher.
(iii) Not only œsophageal but even gastric elements can be included in the lung and develop into gastric cysts.

In this connexion Davis and Salkin (1947) reviewed all published cases of intrapulmonary gastric cysts and added one of their own making a total of 26. They suggest that this type of cyst may be due to embryonic diverticula of the alimentary canal or to intrathoracic vestiges of the vitelline duct. 22 of the 26 were in children under 4 years of age and it is interesting to note that peptic ulceration was present in 7—actually in the cyst.

(*c*) *Of Mixed Respiratory and Intestinal Elements*

II. Mechanical Cause

(*a*) *As Primary Cause*

Rizzi quotes as an example a cyst originating from the bronchial lumen from which it had become mechanically separated by a nubbin of lymphatic tissue. Morelli found lymphatic formation near cysts which had caused dislocation of small amounts of bronchial mucosa.

(*b*) *As Secondary Cause*

Compression of bronchus: check valve causing dilatation, then collapse; the bronchial mucosa then secretes, resulting in a fluid cyst. If this should rupture into a bronchus the cyst becomes air-filled and indeed may be successively a fluid cyst and an air cyst. Vascular compression may cause a cyst to form.

III. Inflammatory Cause

Inflammations of the lung during intra-uterine life are claimed as a potential cause of the formation of congenital cysts.

IV. Neoplastic Process as Cause

Vanzetti found bronchial hypergenesis plus a cyst, the cyst being separate from the main bronchi. Other workers have described a bronchial cystadenoma apparently formed by a kind of neoplastic process. Some of these tumour-like structures, when they contain elements of all bronchial tissues, including cartilage and muscle, are called hamartomas.

Pathology

Most true cysts of the lung have a wall consisting of a fibrous outside layer, a middle layer of collagenous and elastic or muscle strands and a lining of bronchial mucosa. The fluid they contain is mostly mucous but may be gelatinous or albuminous.

Increase in volume of these cysts is thought to be due sometimes to mucosal secretion and sometimes to cellular proliferation.

Various Types and Site of Occurrence

Cysts of the types so far discussed may occur in the lung fields or in the mediastinum.

Parasitic cysts are, of course, uncommon in this country and the only variety likely to be met with is the *hydatid*. Hydatids may occur anywhere in the lungs but they are commoner in the right lung and posteriorly rather than anteriorly. Commencing as round shadows of even density they grow rather slowly and later may lose their round shape. Sometimes a separate pericyst can be seen around the cyst. Air may be visible in the cyst itself or in the pericyst as a result of rupture into a bronchus (Fig. 1).

Of congenital cysts, dermoids have been reported most frequently in the past. They are seen as para-mediastinal round or oval shadows which steadily increase in size (Davidson *et al.*, 1951). They are primarily mediastinal but as they enlarge they are displaced by the mediastinal organs to one side and thus encroach on the medial borders of the lungs. They are dense and, if oval, their long axis is vertical or nearly so. They may contain teeth and sometimes calcify. They are rarely lobulated.

Most of the other cysts in the list are very rare and have no distinguishing features except that thyroid cysts are usually mediastinal in location and tend to calcify and lymphatic cysts are often

multiple in a chain formation. Alimentary type cysts of either œsophageal or gastric origin which contain evidence of all the layers of the alimentary canal are extremely few but characteristically lie posteriorly in a paravertebral situation. Cysts of pericardial origin are interesting. They may lie close to the pericardium or at some distance from it in the lung. They frequently do not reflect cardiac pulsation. I have seen only three of the juxta-pericardial variety but each showed a feature which is possibly characteristic, namely, a narrow translucent layer between the cyst and the pericardium proper (Fig. 2). This is probably a layer of fat and is only visible when the plane in which it lies is brought into the plane of the incident ray by rotation of the patient. Pericardial cysts have a predilection for the right side and have to be differentiated from pericardial hernia, tumour and encysted effusion. Pleural cysts may be either air or fluid in content and often contain tissue of near-by organs, e.g. œsophagus, trachea, pericardium, bony thorax and diaphragm. The fluid type is often best seen after a pneumothorax or pneumoperitoneum has been induced (Cruickshank and Cruickshank, 1951). Pleural air cysts are often multiple, and look the same radiologically as subpleural emphysema, consisting of a group of annular shadows forming a "soap-bubble" appearance. Finally, there is the group of *sero-mucinous cysts*, or as they are alternatively called, bronchiogenic cysts. The latter appellation is perhaps not strictly accurate because although most of these lesions are lined by epithelium of bronchial type, there is some evidence that this can arise by metaplasia of non-bronchial cells, for example, alimentary canal epithelium. It is to this group of sero-mucinous cysts particularly, that the innumerable theories of origin have largely been applied.

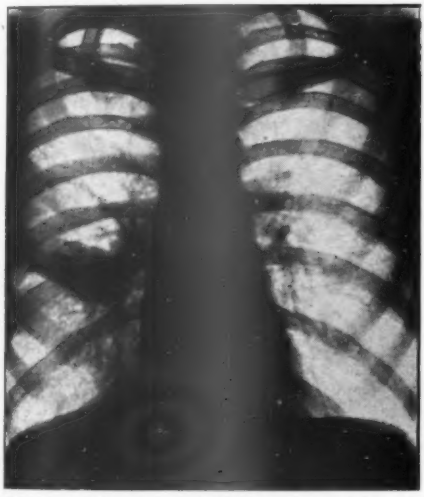

FIG. 1.—Hydatid cyst of right lung, containing air.

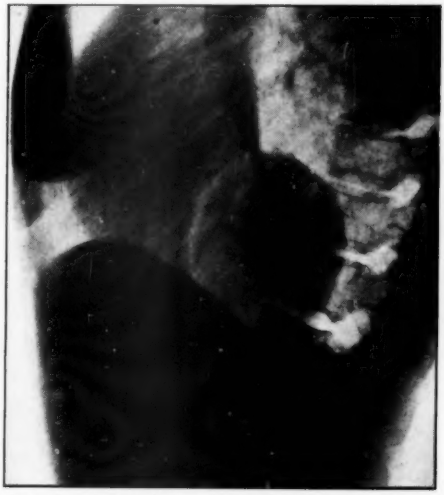

FIG. 2.—Pericardial cyst showing translucent zone between cyst and pericardium proper.

THE INFLAMMATORY HYPOTHESIS

Progress in any branch of the biological sciences is dependent on a continual process of rejection and renewal of observation, experiment and theory. Accordingly, I do not claim that the inflammatory hypothesis, which I now propose to outline, is either the whole or the permanent truth. As yet, we know little of the mechanism of the flow of tissue fluids in the lung and still less of the aerodynamics. We *are* able to appreciate, however, particularly by radiological methods, that anything which interferes with the natural freedom of a bronchus to dilate and contract, may produce the effect of a check valve which allows air into the lobe or segment on inspiration but prevents complete expulsion of the air on expiration. In these circumstances, a zone of lung which may be a lobule, a segment or a lobe—depending on the size of the bronchus involved—becomes progressively distended. This condition is known as obstructive emphysema and is a recognized manifestation of endobronchial tuberculosis in infants and less commonly of endobronchial carcinoma in adults. In both these diseases, a major bronchus is affected and correspondingly the obstructive emphysema usually involves a whole lobe.

At the opposite end of the scale a large number of bronchioles may become obstructed as in asthma with alveolar distension resulting in the asthmatic patient's typical inability to achieve complete expiration.

Between these two extremes, the condition may affect bronchi of intermediate sizes, with hyperinflation of a lobule or a sub-segment, resulting in the production of a ring-shaped shadow, a thin-

walled air-containing cavity. This can and frequently does occur during an acute respiratory illness especially in the pneumonias. Snow Miller (1947) has described what he calls "key points" in lung structure. One such is the point at which the small bronchus or bronchiole divides. This particular point is distinguished by two features: (1) There is a lymph station or aggregation of lymphoid tissue, a focal point for inflammatory cells, and (2) there is a branched circular muscle. If the lymph station becomes choked with inflammatory cells or if the muscle goes into spasm or if both phenomena occur together, the production of a localized obstructive emphysema or air cyst is facilitated. Such conditions are met with in the pneumonias of childhood and particularly in staphylococcal pneumonia. These acute air cysts were described by Peirce and Dirkse (1937), and in American writings have been called "pneumatoceles".

Most people are agreed on the following features: (1) The radiological appearance is that of a circular air-filled cavity with a sharp thin border. Sometimes there is a fluid level.

(2) The mechanism is a check-valve action of the bronchiolar mucosa. (This is too specific since the same effect can be obtained by changes in tissues outside the lumen of the air passages.)

(3) Pneumatoceles are rarely responsible for symptoms (though if they are large they *can* cause cyanosis, dyspnœa and cough).

(4) They are usually benign and ephemeral, disappearing before or soon after the resolution of the pneumonia. Rare examples have been recorded which ruptured into the pleura and set up a tension pneumothorax.

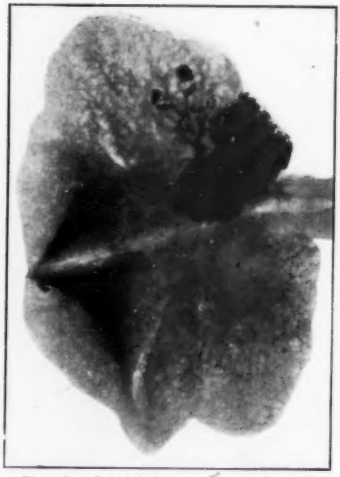

FIG. 3.—Multiple cyst formation after acute inflammatory disease. Lipiodol injection shows two dilated sacs at the ends of small bronchi.

FIG. 4.—Thin-walled bronchiogenic cyst with small amount of contained fluid.

It seems that these "pneumatoceles" are commoner in pneumonias due to staphylococci and may be more frequently encountered in the future as a result of improved survival rates in staphylococcal pneumonia.

Fig. 3 is an example occurring in a baby who died of miliary tuberculosis. At autopsy some of the bronchi were injected with lipiodol and the cysts demonstrated. A histological section showed bronchial epithelium growing into the distended spaces from the bronchi. Had this child survived he might well have had persistent sacs or cysts complete with an epithelial lining.

It thus appears that these cysts are distension sacs and therefore distinguishable from abscesses (which are also common in staphylococcal conditions). Abscesses are said to be produced by necrosis and liquefaction of tissue. Radiologically also, there is a difference. In the formative stage, the cyst is a clear round translucent zone in the midst of an area of consolidation and is seen during the acute stage of the illness: the abscess on the other hand is a sequela of the pneumonia and is revealed as the general consolidation recedes.

In the chronic or persistent stage, the cyst is typically a round, clear zone with a thin, hair-line circumference (Fig. 4). The abscess in this stage may also be round but is less well defined, usually shows some indefinite reaction in the surrounding lung, is more likely to show a fluid level and above all has a thick wall. Another feature which is capable of radiological appraisal is the invariable hyperæmia which accompanies lung abscess but not lung cyst unless the cyst becomes infected.

Bronchiogenic cysts of this type are usually not very large and remain air-filled. They are mostly asymptomatic and found by routine chest surveys.

The bronchial cellular lining, however, may secrete fluid which on the radiograph may appear as a shallow sump (Figs. 4 and 5) or the air may be absorbed and the cyst filled completely with fluid which becomes modified with the passage of time. The lesion responsible for the shadow seen in Fig. 6 was removed at operation and was found to be a bronchiogenic cyst with a bronchial epithelial lining and filled with clear fluid.

Some observers think, however, that subsequent infection is the factor responsible for fluid in a cyst.

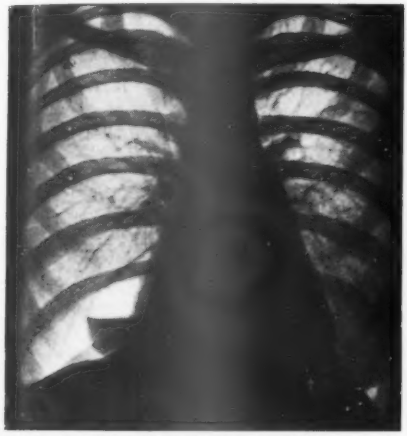

FIG. 5.—Bronchiogenic cyst in right lung of a woman of 28. A film taken one year before did not show the cyst.

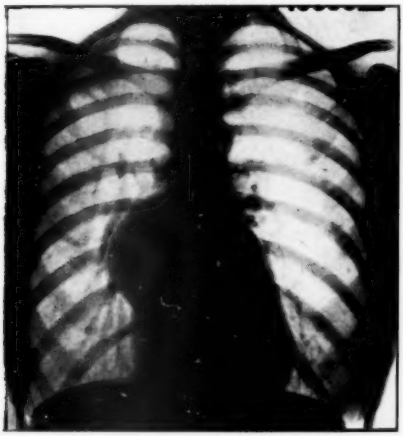

FIG. 6.—Opaque bronchiogenic cyst, confirmed at operation.

RADIOLOGICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

I. Fluid cysts.—These are usually round or oval and of uniform density with a normal surrounding lung. Their shape may be modified by contact with the mediastinum or the walls of the thorax.

Intrapulmonary fluid cysts can simulate bronchiogenic carcinoma which is one reason why they should all be explored in adults. Nevertheless, it is unusual for a carcinoma to be completely round in the absence of hæmorrhage, and carcinoma often shows additional evidence in the form of enlarged hilar glands.

A small or medium-sized hamartoma cannot be distinguished from a fluid cyst. Other confusing lesions are a solitary metastasis, tuberculomata and arteriovenous fistula but there is usually in these cases characteristic clinical information. Tuberculomata contain calcium more often than cysts do whilst tomography or angiography will demonstrate the large vessels associated with vascular lesions.

The diagnosis of opaque cysts which abut on the boundaries of the lung is much more difficult. Shadows which lie in the costovertebral sulcus may be due to neurofibroma. Unless it be possible to show enlargement of the appropriate intervertebral foramen, the matter can be decided only at operation. Although the situation is characteristic of neurofibroma, the same is also true of intrapulmonary cysts of gastric or œsophageal origin.

Cysts situated in a more forward position alongside the mediastinum must be differentiated from mediastinal tuberculomata and thymic conditions.

At diaphragmatic level, lesions which traverse the diaphragm may look like large cysts. Fig. 7 shows a proved bronchiogenic mucus-filled cyst. Radiologically it was practically indistinguishable from another case which at operation was found to be a liver hernia.

Rarely an encysted empyema may mimic a cyst.

II. Air cysts.—These are characteristically hair-line annular shadows, nearly always quite round and situated in the centre of the lung in a para-mediastinal position though, of course, they may occur anywhere in the lungs. They must be distinguished from abscesses, pleural rings and bullæ as well as from rare conditions such as para-sternal hernia. Pleural rings due to temporarily encysted pleural fluid are a not infrequent accompaniment of pneumonia and pleurisy in infants. They disappear usually within a week or two.

Emphysematous bullæ are similar in many ways to air cysts and indeed it is probable that their mechanism of formation is much the same. They can be regarded as distension sacs and may become quite large but they have no complete cellular lining and rarely contain fluid.

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The bronchial cellular lining, however, may secrete fluid which on the radiograph may appear as a shallow sump (Figs. 4 and 5) or the air may be absorbed and the cyst filled completely with fluid which becomes modified with the passage of time. The lesion responsible for the shadow seen in Fig. 6 was removed at operation and was found to be a bronchiogenic cyst with a bronchial epithelial lining and filled with clear fluid.

Some observers think, however, that subsequent infection is the factor responsible for fluid in a cyst.

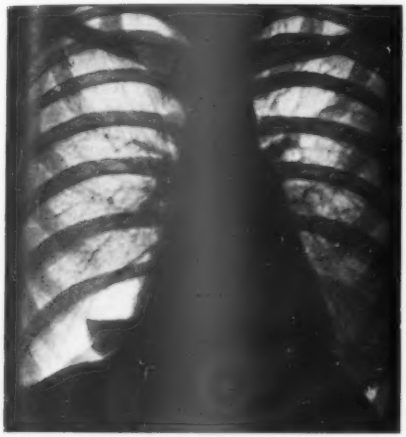

FIG. 5.—Bronchiogenic cyst in right lung of a woman of 28. A film taken one year before did not show the cyst.

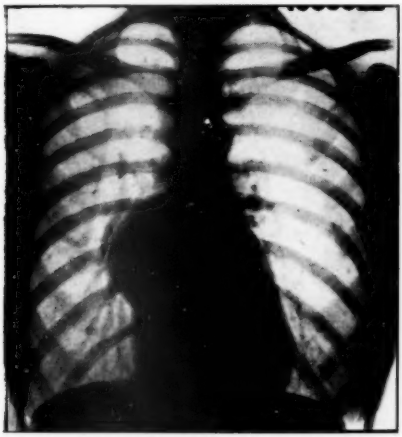

FIG. 6.—Opaque bronchiogenic cyst, confirmed at operation.

RADIOLOGICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

I. Fluid cysts.—These are usually round or oval and of uniform density with a normal surrounding lung. Their shape may be modified by contact with the mediastinum or the walls of the thorax.

Intrapulmonary fluid cysts can simulate bronchiogenic carcinoma which is one reason why they should all be explored in adults. Nevertheless, it is unusual for a carcinoma to be completely round in the absence of hæmorrhage, and carcinoma often shows additional evidence in the form of enlarged hilar glands.

A small or medium-sized hamartoma cannot be distinguished from a fluid cyst. Other confusing lesions are a solitary metastasis, tuberculomata and arteriovenous fistula but there is usually in these cases characteristic clinical information. Tuberculomata contain calcium more often than cysts do whilst tomography or angiography will demonstrate the large vessels associated with vascular lesions.

The diagnosis of opaque cysts which abut on the boundaries of the lung is much more difficult. Shadows which lie in the costovertebral sulcus may be due to neurofibroma. Unless it be possible to show enlargement of the appropriate intervertebral foramen, the matter can be decided only at operation. Although the situation is characteristic of neurofibroma, the same is also true of intrapulmonary cysts of gastric or œsophageal origin.

Cysts situated in a more forward position alongside the mediastinum must be differentiated from mediastinal tuberculomata and thymic conditions.

At diaphragmatic level, lesions which traverse the diaphragm may look like large cysts. Fig. 7 shows a proved bronchiogenic mucus-filled cyst. Radiologically it was practically indistinguishable from another case which at operation was found to be a liver hernia.

Rarely an encysted empyema may mimic a cyst.

II. Air cysts.—These are characteristically hair-line annular shadows, nearly always quite round and situated in the centre of the lung in a para-mediastinal position though, of course, they may occur anywhere in the lungs. They must be distinguished from abscesses, pleural rings and bullæ as well as from rare conditions such as para-sternal hernia. Pleural rings due to temporarily encysted pleural fluid are a not infrequent accompaniment of pneumonia and pleurisy in infants. They disappear usually within a week or two.

Emphysematous bullæ are similar in many ways to air cysts and indeed it is probable that their mechanism of formation is much the same. They can be regarded as distension sacs and may become quite large but they have no complete cellular lining and rarely contain fluid.

It is difficult to define with certainty the boundary between air cysts and bullæ but it is probably safe to say that if the sac is larger than a tangerine it is more likely to be a bulla.

In the presence of a bulla or bullæ, there is, moreover, other evidence of emphysema: the widened rib spaces, depressed diaphragm, &c., and also bullæ, which are frequently peripheral and often basal in situation, become distorted on one side by becoming adherent to adjacent structures (Fig. 8).

Another radiological point of differentiation is that almost invariably bullæ fail to fill with lipiodol, whilst cysts *may* fill depending on the type of opening into the bronchus, the presence of bronchial secretion, &c.

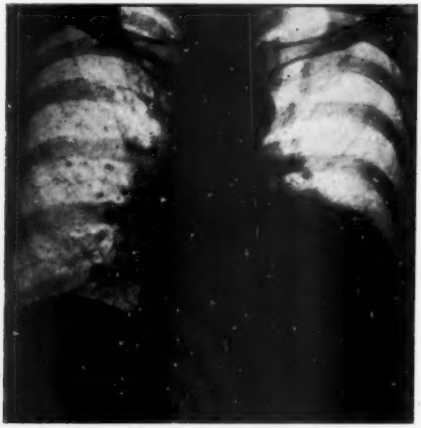

FIG. 7.—Operatively confirmed mucus-filled bronchiogenic cyst in the left lower lobe overlying the heart.

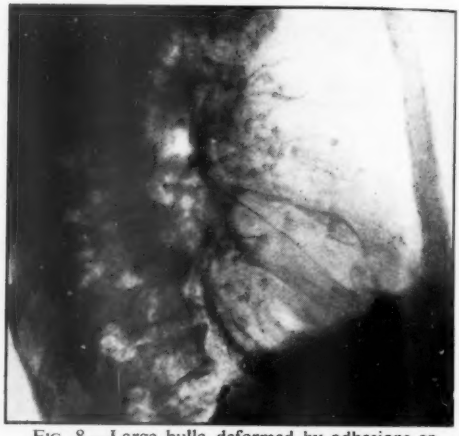

FIG. 8.—Large bulla deformed by adhesions on its diaphragmatic surface.

Para-sternal herniæ may cause some difficulty, but their nature becomes obvious on screening after a barium meal.

Classification of cysts and cystic disease of the lung has never been satisfactorily achieved. Holmes Sellors (1938) suggested the following:

I. Solitary cysts.—(*a*) "Balloon" cysts with raised pressure. (*b*) Smaller cysts—silent unless infected.

II. Multiple cysts.—Medium or small, lobar or scattered, merging into saccular bronchiectasis and honeycomb lung.

Conclusion

In this paper I have tried to avoid encroaching on the larger subject of cystic disease of the lung and have confined my observations to the medium-sized and larger lesions which for the most part are diagnosable only by radiological methods.

Acknowledgments

I am indebted for many of the illustrations and case details to several colleagues including Miss E. K. Abbott of the Sheffield City General Hospital and I particularly wish to thank Mr. Gordon Cruickshank and Dr. James Freer of Leicester.

REFERENCES

Conway, D. J. (1951) *Arch. Dis. Childh.*, **26**, 504.
Cruickshank, G., and Cruickshank, D. B. (1951) *Thorax*, **6**, 145.
Davidson, M., Smithers, D. W., and Tubbs, O. S. (1951) The Diagnosis and Treatment of Intrathoracic Growths. London, p. 28.
Davis, E. W., and Salkin, D. (1947) *J. Amer. med. Ass.*, **135**, 218.
Fontanus (1638) Quoted by Conway (1951).
King, J. C., and Harris, L. C. (1937) *J. Amer. med. Ass.*, **108**, 274.
Koontz, A. R. (1925) *Bull. Johns Hopk. Hosp.*, **37**, 340.
Miller, W. S. (1947) The Lung. Springfield.
Muir, R. (1941) Textbook of Pathology. 5th edition, London.
Peirce, C. B., and Dirkse, P. R. (1937) *Radiology*, **28**, 651.
Rizzi, G., and Lorenzi, O. de (1948) Cisti e Pseudocisti del Polmone. 2nd edition, Faenza.
Schenck, S. G. (1937) *Arch. intern. Med.*, **60**, 1.
Sellors, T. H. (1938) *Tubercle, Lond.*, **20**, 49.

Section of Physical Medicine

President—H. F. TURNEY, D.M., M.R.C.P., M.R.C.S.

[*April* 9, 1952]

DISCUSSION ON INDUSTRIAL RESETTLEMENT

Sir Hugh Griffiths: Industrial resettlement is a big subject with racial, social, economic, and environmental, as well as physical and mental problems.

I propose to discuss only the resettlement of the disabled person. The fate of the disabled person is one that has exercised the mind of mankind almost from the dawn of civilization. There seem to be three alternatives: first that he should become self-supporting; second that he should enjoy the protection of others; or third that he should fail to survive. Until quite recent years a man's ability to rehabilitate himself in industry after injury depended entirely upon his own effort in the majority of cases, the exception generally being the tenants and dependants of the much-maligned landowner classes. In industry, on the other hand, during the Industrial Revolution the physically unfit went to the wall.

The enactment of the workmen's compensation laws at the turn of the century was a step forward in the rehabilitation of the disabled person as it provided some means of sustenance during incapacity for earning as a result of injuries received out of, or in the course of, his employment. The working of these acts with their various modifications indirectly imposed an onus upon the employer to find light work for his disabled personnel and resulted in the first deliberate attempt to resettle in industry temporarily and permanently disabled persons. It also played some part in providing a rough and ready job analysis which was used to interpret the meaning of "light work"—a phrase then without real meaning but invented by lawyers for their delectation and profit. Therefore, the first general move towards resettlement arose by chance from this legislation.

The first attempt at some form of organized resettlement was the formation of the King's Roll after the First World War. This was a scheme by which certain employers received advantages in obtaining Government contracts, &c., if they enrolled as employers of disabled ex-servicemen. The men employed under the King's Roll were mainly messengers, commissionaires and lift attendants. If one should add to these three gatekeeper, timekeeper, night watchman, and "sweeper up", one would have the foundation of the list of jobs designated as light work in the interpretation of the Workmen's Compensation Act.

So far the efforts at resettlement were solely efforts towards placement of disabled persons in employment. The question of training had not arisen. Then largely due to the inspired work of two women, Dame Agnes Hunt and Dame Georgiana Buller, the period between the two world wars saw the foundation of training colleges for the disabled where men and women could be taught trades suitable to their remaining physical faculties. In the establishments called Cripple Training Colleges it was demonstrated with the greatest clarity that no matter what physical handicap existed a disabled person could be taught useful work and thus when Britain was in desperate need of man-power in the last war a large reservoir of potential labour was tapped by careful selection and training of disabled persons.

At the time when the Cripple Training Colleges were tackling the problems of the permanently disabled person, surgery first, and medicine later, turned its attention to the problem of rehabilitation and resettlement of its own patients as part and parcel of treatment. Even before the war links were forged directly between the Seamen's Hospital, Albert Dock, and industrial concerns for this special purpose. Since the war started the success of the liaison between the Birmingham Accident Hospital and Austins, and the Luton and Dunstable Hospital and Vauxhalls, and many other happy combinations, is testimony to the value of these liaisons. So great a success was achieved in the settlement of the disabled persons in industry in the early part of the war that Mr. Ernest Bevin envisaged a state in which all disabled persons could find ready employment. A Committee was set up under the Chairmanship of Mr. George Tomlinson and his report led directly to the passing of the Disabled Persons Employment Act in 1944. This act provided for the re-conditioning, re-training and replacement of disabled persons in industry. It should be seen, therefore, that resettlement which initially depended upon the disabled person's own effort has passed through what I might call three further stages: subterfuge resettlement inspired by the provisions of the Workmen's Compensation Laws, the stage of charitable intervention and, finally, the stage of State protection, although it has not, as far as the disabled person is concerned, reached the stage of State compulsion.

The facilities which exist at present for the resettlement of the disabled can be taken briefly under four headings: (1) the disabled persons employment act; (2) the health service; (3) organized industry; (4) private enterprise.

(1) *The Disabled Persons Employment Act*

The first essential to resettlement under this Act is for the disabled person to have his name entered upon the register of the disabled. Registration implies that he will be unable to do his normal job for at least six months. There are at present just under one million registered disabled persons. The men and women whose names appear upon this register become the special concern of the Disablement Resettlement Officer, or as he is usually known, the D.R.O. At every Labour Exchange throughout the country there is a D.R.O. who is provided with a list of industries and all available occupations in his district, and also with the list of registered disabled persons in that district. He is also supplied with a medical report on each one and it is his function to place the disabled persons in such employment as the medical report may show that they are fit to do. This function of the D.R.O. is, therefore, primarily one of selection and placement. But his duties do not stop there. If he fails to find suitable employment for a disabled person he must point out to him what benefits exist under the Act for his rehabilitation. He may be sent to a re-conditioning centre, where his general physical condition may be built up. He may be sent to a medical centre primarily concerned with the improvement of his nervous state. He may be offered training in a new occupation suited to his physical condition. Such training may be given at one of the training colleges for the disabled or at one of the government training centres. Finally, if it is thought that he will not again become fit for any employment that can be performed under normal working conditions, he may be found employment in a sheltered workshop. There are ninety workshops throughout the country under the auspices of the Ministry of Labour and known as Remploy and these employ nearly six thousand disabled persons, in addition to seventy factories for the blind employing another five thousand. This Act also exercises a certain degree of compulsion upon employers by the "quota" and the "schedule". By the "quota" every employer of 20 or more people must employ 3% of registered disabled persons. By the schedule such employers may employ only disabled persons upon any occupation which is designated in the schedule, and persons so employed do not count towards the quota. At present there are only two such scheduled occupations—car park attendant and passenger lift operator.

(2) *The Health Service*

The health service plays its part in resettlement (1) in providing that treatment that is calculated to restore the man to his capacity for work; (2) in providing the data which are necessary for the D.R.O. to secure proper placement and (3) in providing appliances, such as trusses, artificial limbs, &c., which may be necessary for the man's rehabilitation. The Health Service also provides direct links with the Ministry of Labour through the almoner on the one side and the D.R.O. on the other. They not only have the normal liaison functions but also bring principals together, arranging meetings between the consulting staff of hospitals and the D.R.O. of the Labour Exchange, or sometimes, as in my own case, with principals of local industries.

(3) *Organized Industry*

Organized industry, as for example the Coal Board, have set up their own rehabilitation centres for men who have finished their active hospital treatment and who are not yet fit to be reabsorbed into industry. Other large organizations have established direct contact with hospitals so that treatment can be continued in their own rehabilitation workshops under the direct care of their own industrial medical officers with the advantage of consultations with the hospital consultants.

(4) *Private Enterprise*

A large number of disabled persons are still finding suitable work largely through their own seeking with private individuals and with small firms without invoking the aid of the register on the one hand or the quota on the other. Others are self-employed.

The Position of the Doctor in Relation to Resettlement

The doctor occupies the same position in the health scheme as does the D.R.O. in the Ministry of Labour, and in fact he might just as well claim that title. The D.R.O.'s duty is to ascertain the required physical and mental capacity necessary for a workman in a particular job and then to accept the estimate of physical and mental capacity given to him by the doctor so that he may place him in appropriate employment. In fact it is a case of double analysis: on the one hand, on the doctor's part, analysis of function, and on the D.R.O.'s part, job analysis.

It is exactly five years ago since I last opened a discussion for the Section of Physical Medicine and the subject then was the analysis of function. I said then that "able-bodiedness is a matter of physical function, not of shape, size or stature, and physical functional analysis is the determination of the coefficient of able-bodiedness. Physical function is an expression of thought through muscular action. It follows, therefore, that a complete analysis of physical function in any human being would be as impossible of achievement as the tale of his every thought. A practical analysis must therefore be attempted within certain limits. When I first used the phrase 'physical functional analysis' many years ago I was concerned solely with the fitting of the disabled into industry and was attempting to

assess only those functions which would be in common use in industrial processes"; and ultimately I compiled the following list of primary functions—balancing, running, jumping, climbing, kneeling, stooping, crouching, reaching, throwing, lifting, pulling, pushing, striking, carrying, humping, handling, fingering, cutting with scissors, feeling. Some of these functions are, in fact, composite, but for simplicity's sake may be deemed to be primary.

A complete analysis of all these primary functions fails to give a clear picture of the man's capacity for specific work. Other general considerations of his physical state must be examined. The first of these is stamina. Has the man the power of physical endurance to enable him to work the normal forty-four-hour week? It must be remembered that the hardest man to resettle in industry is the man who can only work broken time.

Next comes the question of physical strength. Can the man withstand a physical strain equivalent to the lifting of a 56-lb. weight, which covers one of the definitions of heavy work?

And then again, how will the man react to different external conditions? Can he withstand exposure to the weather or extremes of heat and cold? Is he by temperament suited to work in crowds or alone, in moving traffic, or in the noise and bustle of a factory?

The doctor's final part, therefore, in the resettlement of the disabled is to present a physical functional analysis to the D.R.O. as an exact piece of work with the very minimum of medical opinion and the very maximum of physiological fact; and this presentation must be made in simple English. It should not be attempted unless the physician is prepared to make a thorough examination of his patient. Such an examination can be undertaken by any painstaking general practitioner or industrial medical officer. Only in very exceptional cases is it necessary to call in the opinion of a specialist in order to complete the physical functional analysis on the lines which I have outlined.

Unfortunately there is no counterpart in industry of this physical functional analysis. Job analyses of many kinds exist but none which are based upon pure physical function. After seeing a medical gymnast taking a class of seriously disabled patients, perhaps some with collapsed lungs and some with legs or backs in plaster of Paris, no D.R.O. or industrialist or trade union leader could be left in any doubt about the capacity for effort, even if he remained unconvinced of the capacity for work. One of the greatest difficulties that has to be overcome by the replacement officer is in convincing both patient and employer that there is nothing unique about the effort necessary to perform his particular type of work. An exaggerated idea of the exclusiveness of *work* has grown up. It may be worth while pausing for a moment to consider the difference between routine work and leisure time occupations—the difference between work and leisure. Three people may be an accountant, bricklayer or actress and their leisure spent in gardening, politics or sewing. Another three may be gardener, politician, or seamstress and their leisure spent as church accountant, bricklaying, or amateur theatricals. The fact is that there is no leisure-time occupation that is not somebody's daily work. In fact, the only difference between work and leisure is that you are paid for one and you pay for the other.

Although I have found it convenient first to consider functional analysis the final step taken by the doctor in his effort towards resettlement of his patient in industry I want now to look back for a moment to the time when the patient first comes under his care. If, as I believe, "the aim of treatment is the restoration of capacity for work and resettlement in industry", then it is imperative that the doctor shall understand the requirements of work. In most cases of illness or injury there is a choice of methods of treatment. The selection of the method that will lead most directly to employment is one that needs great experience, and a variety of questions must be answered before the doctor finally selects the particular form of treatment. I will mention only one. How long can the patient afford to be out of work without suffering such loss of skill, dexterity, and training as will render him temporarily or permanently unfit for his pre-accident work even if his physical defects have been cured? Or again, how long is the surgeon justified in pursuing conservative treatment? Obviously the answer must depend upon the circumstances of the individual patient.

In the Mackenzie Lecture of 1948 I quoted a case of a boy of 14 who had his right hand severely mangled in machinery and whom I first saw three years later: three years which had been spent in continuous treatment by the plastic surgeons and which was not yet completed. At the time I stated:

> "Now what of the patient himself? He was of fairly good physique, now rather run to fat, but, as his father puts it, he is "no scholar". School, in fact, "did not agree with him", and his entry into industry at the age of 14 marked for him escape from the thraldom of uncomprehended letters. He was eager to declare his manhood, to "muscle in" with his fellows into the strife that was his birthright. Three long years have now gone by, three years of daily contemplation of a pitiful and puny limb, hideous alike in its appearance and in its uselessness. Had that hand been amputated at once a modern prosthesis would have enabled the boy to return to his work in a few weeks, still rejoicing in his strength and brim-full of the enthusiasm of youth. But now what is left but a tale of lost incentive, lost interest and lost opportunity?"

The doctor must play a part, and perhaps the most important part, in the resettlement of the disabled in industry. It is for him to plan and carry out treatment with a view to restoring the capacity for work. When carrying out that treatment it is for him to maintain the morale of his patient. Finally, it is for him to assess his patient's capabilities—not disabilities—and lastly it is for him to sell his patient to industry through the D.R.O.

Dr. A. A. Eagger: The physician who is practising medicine in industry is directly concerned with placement—the process by which any worker is chosen and assigned to the job that will most fully utilize his skills, and will at the same time be compatible with his physical capacities and protective of his health and safety. This duty is of particular importance in the case of the disabled, but all who undertake curative treatment must share this responsibility—for successful placement after illness or injury is surely the criterion of cure.

Success in resettlement frequently depends on early and effective rehabilitation which in turn depends on efficient initial treatment, and this will be more readily appreciated if we accept Kessler's definition of rehabilitation as the restoration of the handicapped to the fullest physical, mental, social, vocational, and economic usefulness of which he is capable. This definition indicates the factors other than physical which have a direct bearing on both rehabilitation and resettlement.

The importance of the mental or psychological aspect will be readily recognized; in effect, the attitude to work and the will to work. One man overcomes gross disability and leads a happy and useful life, the other with a comparatively minor disability is unemployed. I saw a very good example of this the other day in one of our member firms where the resettlement of a man after treatment for duodenal ulcer was causing difficulty. A co-operative management had initially gone to considerable pains to provide suitable employment well within his mental and physical capacities and with a good financial return, but he was disgruntled, dissatisfied, and constantly asking for change of employment. Within twenty feet of where this man was working I saw a totally blind man working a capstan lathe and using a Braille micrometer. I was assured that his rate of production was equal to that of the able-bodied men on the same job, and it was obvious that he was happy and found his work completely satisfying, but it was also obvious that the management took considerable pride in this man, and their attitude to him was totally different from that to the other. They could comprehend the degree of disability and their sympathies were roused to do their utmost for him, but they could not appreciate the disability of the man with the psychosomatic condition and their attitude, quite understandably, was becoming antagonistic.

This attitude of management to the disabled is in many ways the crux of the problem, for in the end the success of all the efforts of the team who are responsible for a patient's restoration to working capacity depends on the co-operation of management in the reinstatement of the individual in suitable work.

The occupational history prior to the onset of disability may be of value in indicating the patient's attitude to work, particularly if in a time of full employment it is found that the individual concerned has had long periods of unemployment, or frequent changes of occupation.

Age must be taken into consideration; the young may never have acquired the habit of work, while the elderly may have become discouraged by repeated failures either to obtain work or to hold a job when they get it, particularly when the diseases associated with advancing years are added to their existing disability and tend to limit even further their power of adaptation to new circumstances.

The social background and standard of intelligence will obviously affect the position, as the skilled and intelligent worker can usually be more easily resettled than the man whose previous occupation was unskilled. The single man, with no home other than the common lodging-house, and the improvident married man, who, regardless of consequences, continues to father an increasingly large family, present equally difficult problems.

The availability of suitable work in the area in which the man lives may be an important factor. At Slough we are fortunate in having a wide variety of light industries in which it is frequently possible to place disabled workers in jobs where their ability can be used to the full.

A new difficulty is now being encountered which is directly attributable to our social legislation by which, owing to the various benefits which a disabled man may obtain from the State, there may be little or no financial incentive for him to obtain work. This is an example of a case referred to our Recuperative Centre at Farnham Park only the other day, and illustrates certain factors to which I have already referred. A man engaged in the somewhat uncongenial occupation of a sewer worker, aged 36, strained a muscle in his back while at work in October 1949. The most careful investigation in a well-known hospital had revealed no cause for the backache of which he complains. He has seven children aged from 14 years to 1 year. He has been unemployed since the date of the injury and has never made a serious attempt to get a job, though both almoners and D.R.O.s have gone to considerable trouble to obtain suitable work for him. This man is at present getting each week:

	£	s.	d.
Unemployment Benefit	3	7	0
National Assistance Board Allowance	2	14	0
Family Allowance	1	10	0
Ministry of National Insurance Special Hardship Allowance	1	0	0
A total of	£8	11	0

What financial incentive is there for this man to work? This is by no means an isolated case and illustrates at least one defect in our conception of the Welfare State.

The nature of the disability must of necessity have a direct influence on resettlement. It may be ...ic and obvious or progressive and hidden. The man who has lost a limb or an eye tends to accept his disability and do his utmost to overcome it; his disability is recognized and usually he has received some form of financial compensation. The medical case on the other hand may have comparatively little to show; his disability is not appreciated either by management or his fellow-workers who may even object to his inclusion in the working community out of ignorance or fear, while he himself becomes embittered and despondent.

These then are some of the factors which I suggest must be taken into consideration when we are attempting to resettle a patient after illness or injury. It is not therefore surprising that a variety of methods have been devised to find some solution to the problem of matching workers and jobs—this is in itself an indication of the complexity of the problem and of our failure to find a completely satisfactory formula.

Bert Hanman, the industrial psychologist, states that selective placement for the handicapped is a fabrication, its philosophy is obsolete, its history one of bewilderment and its practice withering. He suggests that we need fresh perspectives and more enlightened principles. With the majority of the authorities in the United States he is of the opinion that the quota system which we have adopted —by which all firms employing over 20 men have to include 3% of disabled in their number of workers—tends to segregate and not integrate the disabled in the working community.

While we may not be prepared to accept this hypothesis, there is certainly little reason to regard our present methods with complacency, and greater efforts must be made to achieve a better understanding of the problem and to advance a practical solution.

The first step in resettlement is a correct evaluation of the patient's ability to enable a decision to be taken as to whether he can be placed directly in industry in suitable work, or to refer him for re-training. In firms which have an industrial health service the medical officer will be aware of the standard of physical fitness required for any particular job and, ideally, may have at his disposal a job analysis; with his co-operation placement can be more easily carried out. The great majority of patients have, however, to be resettled in firms which have no industrial health facilities. The Disablement Resettlement Officer may have made contact with the patient in hospital, but, if not, the procedure then is to advise the patient to apply to the local office of the Ministry of Labour and National Service in order to be placed on the Disabled Register and to complete for him the form D.P.1, which assesses the disability on a functional rather than on an anatomical basis. This form has been subjected to considerable criticism in spite of its distinguished parentage, and I freely admit that in the early days I was myself critical of its value. In particular, I felt that it did not sufficiently stress the residual ability or give sufficient indication of the nature of employment which might prove suitable. My opinion, however, has altered since I made an unsuccessful attempt to produce an alternative form with the same objective—namely, to produce a report on working capacity which could be readily understood by a layman, in this case the Disablement Resettlement Officer. Providing a careful physical examination has been carried out, and this is essential, the actual completion of the form only takes a few minutes, while every effort has been made to reduce the amount of writing to the minimum, and I would emphasize that an opportunity is given to state what action you recommend should be taken in the particular case.

A memorandum from the Ministry of Health states that the responsibility for assessing disability and advising on residual capacity and suitable conditions for work belongs to the medical profession, the responsibility for placement in work rests with the Disablement Resettlement Officer. The D.R.O. is said to be there for his knowledge of industry. His task is certainly a difficult one and, from what has already been said, you may agree that knowledge of industry is not the only factor in successful placement, albeit an important one. The D.R.O. has my full sympathy and I have met a few of outstanding ability, but I venture to suggest that the D.R.O. is frequently the weakest link in the chain. In the Slough Industrial Health Service we have recently initiated a social service department under the charge of an experienced hospital almoner, one of whose main duties is to co-operate with the D.R.O. in placement of disabled workers. We feel that with her knowledge of the social background of patients, her experience in a large teaching hospital, and the close contact which she now maintains with industry, she will do much eventually to ensure a more satisfactory placement of workers after discharge from our Rehabilitation Centre. The value of the almoner now that she is able to carry out her proper function is, I think, universally recognized, but I suggest that her value could be enhanced if she could be given an opportunity of gaining a wider knowledge of the industrial environment.

In the annual report of the Ministry of Labour and National Service for 1950 it is stated that the primary object of the Disablement Resettlement Officer Service is to find employment for the disabled person that is best suited to his disability. While I feel this should read "to his ability" it is only fair to state that during the year 1950 nearly 170,000 registered disabled persons were placed in employment by local offices of the Ministry of Labour. When the D.R.O. finds difficulty in placing a case for medical reasons, he can refer the worker to the Medical Interviewing Committee of the hospital. These committees normally consist of a member of the hospital staff with special knowledge of rehabilitation,

an industrial medical officer, an almoner, and the D.R.O. I suggest that the potentialities of these committees have not been fully realized and that a greater number of cases could be referred to them with advantage.

The success of any scheme of resettlement can only be assessed if an efficient follow-up scheme is instituted. The following figures are from the Ministry of Labour report: in the quarter ended December 30, 1950, 6,964 cases were followed up—73·7% were satisfactorily placed, 4·9% were in employment which was not regarded as satisfactory, 10·4% were unemployed, and 11% failed to reply. One would hesitate to deduce much from these figures, nor do I think that the figures of 936,500 on the Disabled Register—of whom 57,418 are known to be unemployed—give a true picture of the position.

There are other resettlement methods which have been tried in particular industries and, on a wider basis, in the United States. The simplest of these, but by no means the most successful for obvious reasons, is the trial and error method. A man given a job beyond his capacities becomes disheartened, and may be unwilling to try again. The disability method consists of classifying the disabled into groups according to their particular disability, e.g. the one-armed, &c., and preparing by job analysis a list of jobs which workers with this particular disability should be able to perform—here again the emphasis is on the disability and not the ability.

Some industries have adopted a modified PULHEEMS system with varying degrees of success. This system was initiated by the Canadian Army and has now been adopted by the British Army for the examination of all intake, and is an example of the rating method which has found favour in certain industries.

Bert Hanman's own method is apparently used in the United States, but as far as I am aware has not been adopted to any extent in this country. It depends in the first place on an accurate job analysis being carried out by an experienced job analyst, in which the hour is used as the standard unit, e.g. a particular job might entail standing for three hours, sitting for one hour, lifting a known weight for two hours, and so on in an eight-hour shift. A master chart is made up to show the physical and environmental demands of each job. The medical officer reports the worker's physical capacities on a form which is designed and made up to register exactly with the master chart. By placing this form in position on the master chart and sliding it up and down, the worker's capacities can be compared with the job's demands.

This method is, of course, to be used for the placement of all workers, as Hanman insists that the great majority of workers have some physical handicap and that our objective is to ascertain the occupational handicap, if any. This method is certainly an ingenious approach to the problem of placement, but it again is concerned with the physical demands of the job and does not take into account some of the other factors on which successful placement depends. Further, it does entail a job analysis being carried out by a trained job analyst, and this in itself presents a practical difficulty in small firms.

While it is obviously an advantage if the disabled person can be placed in the firm by which he was previously employed, ideally in his previous occupation or one closely allied to it, with a large proportion of cases this is impossible in small firms where the variety of occupations may be strictly limited. The man himself normally prefers to get back to an environment which he knows and with workmates with whom he may have been associated for years, while management may feel a moral responsibility towards an old and valued employee. If re-employment can be provided by breaking down a particular process or adapting a machine, the result may be entirely satisfactory, but if stop-gap employment such as cleaner or caretaker is all that can be offered, it is probably wiser to try and place the disabled man where work of a more satisfying nature can be provided with greater security, though it may entail the severance of former associations.

The problem is certainly complex but surely this is a challenge to all of us who have the interests of our patients at heart.

In our endeavour to promote the welfare of workers, whether it be by treatment or satisfactory placement, we seek the co-operation of all—and in particular of those who are fortunate enough to have gained specialized knowledge and experience in the sphere of physical medicine.